Date: January 31, 2008

From: Karen M. Farizo, M.D.
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Center for Biologics Evaluation and Research
Food and Drug Administration

Subject: Clinical Review of KINRIX Biologics License Application

To: BLA STN# 125260

Through: Lucia Lee, M.D.
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Food and Drug Administration

cc: Michael Schmitt, PhD
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1 General Information

1.1 Medical Officer Review Identifiers and Dates

1.1.1 BLA #: 125260

1.1.2 Related INDs and BLAs

- GlaxoSmithKline (GSK) Biologicals' Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine (DTaP-IPV)
  - IND -------
- GSK Biologicals' INFANRIX (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) (DTaP)
  - BLA STN 103647: INFANRIX approved for four consecutive doses in children ages 6 weeks through 6 years, January 1997
  - BLA Supplement STN 103647/5001: INFANRIX approved for fifth consecutive dose, July 2003
  - IND -------
- Novartis Vaccines and Diagnostics GmbH & Co.'s BL 103648 for the manufacture of Diphtheria and Tetanus Toxoids Adsorbed Combined Bulk (For Further Manufacture)
  - approved January 1997
  - BLA Supplement STN 103648/5046: 2-Phenoxyethanol-free formulation approved May 2005
- GSK Biologicals' PEDIARIX [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined] (DTaP-HepB-IPV)
  - BLA STN 103907: PEDIARIX approved for three dose series in December 2002
  - IND -------
- GSK Biologicals' BOOSTRIX (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed) (Tdap)
  - BLA STN 125106: BOOSTRIX approved for single booster dose in persons ages 10-18 years, May 2005
  - IND---------
- ----------

1.1.3 Reviewer Name, Division, and Mail Code

Karen Farizo, M.D.
Division of Vaccines and Related Products Applications
HFM-475

1.1.4 Submission Received by FDA: 4/9/07

1.2 Product

1.2.1 Proper Name: Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine

1.2.2 Tradename: KINRIX

1.2.3 Product Formulation

Table 1. KINRIX formulation per dose

Ingredient	**Quantity (per 0.5 ml dose)**
Active ingredients	
Diphtheria toxoid	25 Lf
Tetanus toxoid	10 Lf
Pertussis toxoid (PT)	25 µg
Filamentous Hemagglutinin (FHA)	25 µg
Pertactin (PRN)	8 µg
Inactivated poliovirus type 1	40 D-Antigen Units
Inactivated poliovirus type 2	8 D-Antigen Units
Inactivated poliovirus type 3	32 D-Antigen Units
Excipients	
Aluminum hydroxide (adjuvant)	---------
NaCl	150 mM
Water for injection	q.s ad 0.5 ml

Source: 125260/0.0, m3.2.P.1, page 1

1.3 Applicant: GSK Biologicals

1.4 Pharmacologic Class: Vaccine

1.5 Proposed Indication: A single dose in children 4 through 6 years of age for active immunization against diphtheria, tetanus, pertussis, and poliomyelitis as the fifth dose in the DTaP series and the fourth dose in the inactivated poliovirus vaccine (IPV) series.

1.6 Dosage Forms and Routes of Administration: KINRIX is a liquid suspension for intramuscular injection. The vaccine is presented as a 0.5 mL monodose preparation either in prefilled glass syringes or in glass vials.

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3 Executive Summary

With this BLA, GSK Biologicals is seeking approval of their DTaP-IPV vaccine administered as a single intramuscular dose in children 4-6 years of age who have previously received four doses of DTaP vaccine and three doses of IPV. The proposed tradename for the DTaP-IPV vaccine intended for use in the U.S. is KINRIX. The formulation of KINRIX was provided in Table 1. The DTaP component of KINRIX is identical to GSK Biologicals' INFANRIX as well as the DTaP component of PEDIARIX, both licensed in the U.S. The IPV component of KINRIX is identical to that contained in PEDIARIX.

There is no generally accepted serological correlate of protection for pertussis. The efficacy of the pertussis component of KINRIX was previously demonstrated in clinical studies of INFANRIX administered as a three dose series in infants. The primary evaluation of the immunogenicity of the pertussis component of KINRIX administered as a booster dose in children 4-6 years of age was based on a comparison of pertussis booster responses, relative to children who received a booster dose of INFANRIX. There are well accepted serological correlates of protection for diphtheria, tetanus, and the polioviruses contained in KINRIX. However, a high proportion of children 4-6 years of age who previously received four doses of DTaP vaccine and three doses of IPV are expected to have seroprotective levels of anti-diphtheria, anti-tetanus, and anti-poliovirus type 1, type 2, and type 3 antibodies prior to receipt of their subsequent dose of DTaP vaccine and IPV. For these antigens, the primary evaluation of the immunogenicity of KINRIX administered as a booster dose in children 4-6 years of age was based on a comparison of diphtheria and tetanus booster responses and GMTs of antibodies to the three polioviruses, relative to children who received separately administered INFANRIX and IPOL (U.S. licensed IPV, Sanofi Pasteur, SA). The evaluation of the safety of KINRIX was based on a comparison to separately administered INFANRIX and IPOL.

In total, three clinical studies were conducted to evaluate GSK Biologicals' DTaP-IPV vaccine when administered as a booster dose to healthy children 4-6 years of age who previously received four doses of DTaP vaccine (children in two of the clinical studies received four doses of INFANRIX) and three doses of poliovirus vaccine (see Table 2). The objective of the clinical development program was to evaluate the immunogenicity and safety of DTaP-IPV in this age group, compared to separately administered INFANRIX and IPOL.

The clinical development plan consisted of one pivotal phase III study (Study 213503/048) to evaluate the safety, immunogenicity and lot-to-lot consistency of KINRIX and two supportive studies, Study 213503/046 and Study 213503/047 (see Table 2). The formulation of the DTaP-IPV vaccine evaluated in the two supportive studies was the same as that of KINRIX with the exception that it also contained 2-phenoxyethanol as a preservative. The two supportive studies provided supportive safety data. Study 213503/047 also provided supportive polio immunogenicity data. Studies 213503/047 and 213503/048 were conducted in the U.S. Study 213503/046 was conducted in Australia. All three studies were controlled and randomized. A total of 3,537 subjects received a single dose of GSK Biologicals' DTaP-IPV vaccine as part of this clinical development program. Of these subjects, 3,156 (89%) received KINRIX in Study 213503/048. Across the three studies, a total of 1,434 Control subjects received separately administered INFANRIX + IPOL, including 1,053 subjects from Study 213503/048.

In Study 213503/048, all subjects had previously received four doses of INFANRIX and three doses of IPOL. Subjects were randomized to one of four groups: one of three lots of KINRIX or U.S. licensed Control vaccines (INFANRIX + IPOL). All subjects received MMR_{II} (U.S. licensed Measles, Mumps, and Rubella Virus Vaccine, Live, Merck & Co., Inc.) concomitantly with KINRIX or Control vaccines. In this study, manufacturing lot consistency of KINRIX was

demonstrated for the diphtheria, tetanus, and pertussis antigens and the polioviruses contained in the vaccine, by evaluation of post-vaccination antibody GMTs or GMCs according to pre-specified equivalency criteria. KINRIX was shown to be non-inferior to separately administered INFANRIX + IPOL with regard to post-vaccination booster responses for diphtheria, tetanus, and the pertussis antigens and antibody GMTs for the three polioviruses. Non-inferiority criteria for these analyses were pre-specified.

All monitored safety parameters were taken into account in evaluating the safety profile of KINRIX. In Study 213503/048, information on the occurrence and severity of injection site pain, redness, swelling, and increase in mid-upper arm circumference within four days (Days 0-3) after vaccination was recorded daily by the subjects' parents or guardians. Within four days post-vaccination, injection site pain, redness, swelling, and increase in mid-upper arm circumference at the DTaP-based administration site was reported by 57%, 37%, 26%, and 36% of KINRIX subjects, respectively, and by 53%, 37%, 27%, and 38% of Control subjects, respectively. During this period, pain (at the KINRIX or INFANRIX injection site) that prevented normal activities was reported in 1.6% of KINRIX subjects and 0.6% of Control subjects. The incidence of any pain and of pain that prevented normal activities were statistically significantly higher (p-value <0.05) at the KINRIX injection site than at the INFANRIX injection site. Rates of the other solicited local reactions at the KINRIX or INFANRIX injection sites were not statistically significantly different between groups.

Increased circumferential swelling, defined as injection site swelling involving >50% of the upper arm length and associated with a >30 mm increase of the mid-upper arm circumference, within four days following vaccination, was reported for the KINRIX injected arm in 0.6% of subjects and for the INFANRIX injected arm in 1.0% of Control subjects. Based on pre-specified criteria, KINRIX was non-inferior to INFANRIX with regard to increased circumferential swelling within four days following vaccination.

Body temperature was monitored daily for the 15 day period post-vaccination. Within four days post-vaccination (Days 0-3), 6.5% of KINRIX subjects and 2.1% of Control subjects reported fever >38.0^{o}C (p-value <0.05). Rates of fever >38.5^{o}C, >39.0^{o}C, >39.5^{o}C, and >40.0^{o}C were not statistically significantly different between groups.

No deaths were reported among subjects during any of the three studies. Across the three studies, serious adverse events within 30 days post-vaccination were reported in three DTaP-IPV subjects (cerebrovascular accident; hypernatremia and dehydration; and dehydration and gastroenteritis) and in four Control subjects (constipation; foreign body trauma; periorbital cellulitis; and fever). The cerebrovascular accident was an ischemic stroke of undetermined etiology that occurred 30 days following KINRIX in a four-year old female in Study 213503/048. This subject was reported to have a strong family history of thrombotic events.

The BLA also included a global review of post-marketing safety surveillance data on GSK Biologicals' DTaP-IPV (formulation distributed outside of the U.S. contains 2-phenoxyethanol) and INFANRIX for identification of events that may have a possible causal association with vaccination. For DTaP-IPV, the review covered a period of approximately 10 years during which approximately ---------- doses were distributed. Based on the review, the applicant identified injection site vesicles and pruritis for inclusion in the post-marketing section of the KINRIX package insert. For INFANRIX, the review covered a period of approximately 13 years during which approximately ---------- doses were distributed. Based on the INFANRIX review, the applicant identified the following events for inclusion in the post-marketing section of the KINRIX and INFANRIX package inserts: anaphylaxis, urticaria, angioedema, apnea, febrile

convulsions, lymphadenopathy, and thrombocytopenia. Other events already listed in the post-marketing section of the INFANRIX package insert include allergic reactions, hypotonic-hyporesponsive episode, and convulsions.

In view of the occurrence of a cerebrovascular accident in Study 213503/048, at the request of CBER, GSK Biologicals provided a review of their global safety database for reports of adverse events following DTaP-IPV, INFANRIX, and PEDIARIX that are medically consistent with cerebrovascular accident, thrombosis, or hypercoagulable states. For this review, global distribution of DTaP-IPV, INFANRIX, and PEDIARIX were estimated to be approximately ---------- doses, respectively. Three reports consistent with diagnostic criteria for cerebrovascular accident were identified and three reports consistent with diagnostic criteria for thrombosis, thromboembolism or hypercoagulable states were identified. For each case, the applicant identified a plausible cause other than vaccination.

The safety and immunogenicity data included in the BLA support approval of KINRIX as a single dose in children 4-6 years of age who have previously received four doses of DTaP vaccine, using INFANRIX and/or PEDIARIX for the first three doses and INFANRIX for the fourth dose, and who have previously received three doses of IPV. Sufficient data are not available to support the safety and effectiveness of KINRIX following vaccination with DTaP vaccines from other manufacturers.

The applicant has proposed to continue monitoring all spontaneously reported large injections site swelling reactions following their DTaP-IPV vaccine, and to obtain by questionnaire standardized, detailed information for all cases. The applicant has proposed enhanced passive surveillance of stroke, hypercoagulable state, thrombus, and thromboembolism to further evaluate any possible association between their DTaP-IPV vaccine and these events. For spontaneous reports of stroke and related events, the applicant has proposed expedited reporting to the FDA.

In Studies 213503/047 and 213503/048, KINRIX was administered concomitantly with U.S. licensed MMR_{II}. The BLA contained no data on concomitant administration of KINRIX with varicella vaccine. The applicant has proposed to conduct a post-licensure study in approximately 400 children 4-6 years of age to evaluate the safety and immunogenicity of KINRIX when given concomitantly with varicella vaccine.

As discussed in Section 9.3 of this review, FDA's Pediatric Review Committee concurred with the recommendation to grant waivers of assessments of KINRIX in the pediatric populations 0-<4 years of age and 7-18 years.

4 Clinical and Regulatory Background

4.1 Diseases to be Prevented and Available Interventions

KINRIX is intended for the prevention of diphtheria, tetanus, pertussis, and poliomyelitis. Available data support the use of KINRIX as a single dose in children 4-6 years of age for the fifth dose of the DTaP vaccine series (following INFANRIX and/or PEDIAIRX for the first three doses and INFANRIX for the fourth dose) and for the fourth dose of the IPV series.

Two DTaP vaccines are currently approved in the U.S. for use as a fifth consecutive dose following four previous doses of the same DTaP vaccine -- INFANRIX and Tripedia (Sanofi Pasteur Inc.). INFANRIX is also approved for use as a fifth dose of DTaP following a series using PEDIARIX for one or more of the first three doses and INFANRIX for the other doses.

Two IPV vaccines currently approved in the U.S. may be used in children ages 4-6 years of age following three previous doses of IPV—IPOL and POLIOVAX (Sanofi Pasteur Limited). Of these, only IPOL is currently distributed in the U.S.

4.2 Previous Human Experience with KINRIX and Related Vaccines

GSK Biologicals markets a DTaP-IPV vaccine, currently approved in 31 countries outside of the U.S. The vaccine is indicated for primary immunization from the age of 2 months against diphtheria, tetanus, pertussis and poliomyelitis and as a booster dose for previously primed children. GSK Biologicals' DTaP-IPV marketed outside of the U.S. contains 2-phenoxyethanol (≤2.5µg per dose). Otherwise, the formulation is the same as that of the vaccine intended for use in the U.S. As of August 6, 2006, ---------- doses of GSK Biologicals' DTaP-IPV had been distributed since first launch in August 1996.

INFANRIX, which is identical to the DTaP component of KINRIX, was first licensed in Germany in 1994 and is currently licensed in 84 countries. In the U.S., INFANRIX was first licensed in 1997 as a 4-dose series and is currently licensed as a 5-dose series in infants and children 6 weeks to 7 years of age.[1] Through July 2006, approximately---------- doses of INFANRIX have been distributed worldwide. In addition, more than ---------- doses of INFANRIX-based combination vaccines (including U.S. licensed PEDIARIX) have been distributed worldwide.

GSK Biologicals' IPV component of KINRIX is not licensed as a stand alone vaccine, but as part of combination vaccines [GSK Biologicals' DTaP-IPV, DTaP-IPV/Hib, DTaP-HepB-IPV (PEDIARIX), and ---------- with more than ---------- doses distributed worldwide. PEDIARIX, which contains the same IPV component as KINRIX, was approved in the U.S. for a 3-dose primary series in December 2002.

4.3 Regulatory Background Information

Chronology of Review:
4/9/07: Application received

5 Clinical Data Sources, Review Strategy and Data Integrity

5.1 Material Reviewed

5.1.1 BLA Files Reviewed

The following files served as the basis for the clinical review:
Study 213503/048 Clinical Study Report
Study 213503/047 Clinical Study Report
Study 213503/046 Safety Synopsis
Risk Management Plan
Requests for Partial Waiver of Pediatric Studies
Clinical Overview
Summary of Clinical Efficacy
Summary of Clinical Safety
Reports of Postmarketing Experience:
    Listing of Post Marketing Events

[1] The formulation of INFANRIX initially approved in the U.S. contained 2-phenoxyethanol (2.5 mg per 0.5 ml dose) as a preservative. The formulation of INFANRIX currently approved in the U.S. does not contain 2-phenoxyethanol.

Safety Pharmacovigilance Summary
Support for Label

5.1.2 Postmarketing Experience

5.1.2.1 Global Review of Postmarketing Safety Surveillance Data

The BLA included a report of a global review of postmarketing safety surveillance data for DTaP-IPV and INFANRIX conducted by GSK Biologicals. The applicant reviews all reported adverse events on an ongoing basis to detect any new safety signal. Data are routinely evaluated in a cumulative manner for a possible causal association with vaccination. To select events for detailed review and analysis, the applicant used two thresholds, one for all events irrespective of seriousness (1 reported event per million doses distributed) and one for serious adverse events (1 reported event per 10 million doses distributed). These thresholds supplement the review of all serious events or events of interest.

Post-marketing surveillance reported adverse events were evaluated for their plausibility to be related to vaccination based on the following criteria: (1) frequency of reporting, (2) time to onset after vaccination, (3) quality of case reports, (4) literature data and reference healthcare organization assessment, (5) adverse reactions identified for similar vaccines, (6) specificity (e.g. dyspnea as a symptom of an allergic reaction was not considered itself as an adverse reaction), (7) distinctness and (8) severity.

For DTaP-IPV, the review covered the period from first launch in 1996 through July 2006, during which approximately ----------doses were distributed. Based on the evaluation, GSK Biologicals identified injection site vesicles and pruritis as events to include in the postmarketing section of the U.S. package insert for KINRIX.

Based on previous postmarketing analyses of INFANRIX, events identified for inclusion in the INFANRIX package insert included allergic reactions (including anaphylactoid reactions), collapse or shock-like state (hypotonic-hyporesponsive episode), and convulsions. The most recent postmarketing analyses for INFANRIX covered the period from first launch in 1994 through July 2006, during which approximately ---------- doses were distributed worldwide. Based on these analyses, GSK Biologicals identified the following events for inclusion in the postmarketing section of the U.S. package insert for KINRIX and INFANRIX: anaphylaxis, urticaria, angioedema, apnea, febrile convulsions, lymphadenopathy, and thrombocytopenia.

5.1.2.2 Review of Cerebrovascular Accident, Thrombosis, and Hypercoagulable State

In Study 213503/048, the pivotal study of KINRIX, one subject reported a serious adverse event of cerebrovascular accident 30 days following receipt of KINRIX (see Section 6.1.2.3.6 for additional clinical information on this event). Subsequent to this report, CBER requested that GSK Biologicals review their global safety database for reports of adverse events following DTaP-IPV administration that are medically consistent with stroke, hypercoagulable states, and thrombosis. GSK Biologicals searched their worldwide safety database using the following criteria:

- Data lock point: January 1, 2007
- Report types: All spontaneous reports, post-marketing surveillance reports, and unblinded serious clinical trial reports for DTaP-IPV, INFANRIX, and PEDIARIX.
- Medical Dictionary for Regulatory Activities (MedDRA) preferred term(s): aphasia, apraxia, cerebral ischaemia, cerebral haemorrhage, cerebrovascular accident, cerebrovascular

disorder; cranial nerve paralysis, diplegia, dysarthria, gaze palsy, haemorrhage intracranial, hemiparesis, hemiplegia, monoparesis, monoplegia, ophthalmoplegia, paralysis, paralytic disability, paresis, quadriplegia, quadriparesis, deep vein thrombosis, embolism, fibrin D dimer increased, necrosis, thrombosis.

For this review, global distribution of DTaP-IPV, INFANRIX, and PEDIARIX was estimated to be approximately ---------- doses, approximately ---------- doses, and approximately ---------- doses, respectively. A total of 34 reports (INFANRIX, n=23; PEDIARIX, n=5; DTaP-IPV, n=6) potentially medically consistent with cerebrovascular accident were identified and the case summaries were reviewed by the applicant. For three of these reports (one each following DTaP-IPV, INFANRIX, and PEDIARIX), the description of the event was considered by GSK Biologicals as consistent with published diagnostic criteria for cerebrovascular accident. Each case was thought by the applicant to have other, more likely causes of cerebrovascular accident than vaccination (family history of thrombotic events and protein C deficiency; dilated myocardiopathy, myocarditis and bilateral cortical infarctions with probable embolic origin; and global cerebral ischemia diagnosed after cardiopulmonary arrest in a patient with sleep apnea). The case following DTaP-IPV was the case from Study 213503/048 that prompted the review.

A total of 6 reports (INFANRIX, n=5; PEDIARIX, n=1; DTaP-IPV, n=0) potentially medically consistent with thrombosis or hypercoagulable states were identified. For three of these reports (two following INFANRIX and one following PEDIARIX), the description of the event was considered by GSK Biologicals as consistent with diagnostic criteria for thrombosis, thromboembolism or hypercoagulable states. Each case was thought by the applicant to have other, more likely causes of these events than vaccination (laryngeal stenosis requiring tracheal intubation; fatal seizure in a patient with a history of neurologic disorder and seizures; and cardiorespiratory arrest). One additional case following INFANRIX, reported as "presumed severe thrombosis" was poorly documented and could not be assessed. For this case, the reporter's assessment of causality was "not related" to vaccine.

5.2 Table of Clinical Studies

Data from three clinical studies of GSK Biologicals' DTaP-IPV administered to children 4-6 years of age were included in the BLA (Table 2). One of the studies, Study 213503/048, is considered pivotal for the evaluation of the safety and immunogenicity of KINRIX. Study 213503/047 provides supportive polio immunogenicity data (also see Section 5.3) and safety data for the evaluation of KINRIX. Study 213503/046 provides supportive safety data for the evaluation of KINRIX.

Table 2. Studies included in the KINRIX BLA

Study (Country)	Previous DTaP, polio and MMR vaccination history	Groups	Total vaccinated cohort Planned/Actual (N)
Non-IND study			
213503/046 (Australia)	4 doses DTaP + 3 doses of IPV, OPV or sequential IPV/OPV during the first 2 years of life; 1 dose of MMR in 2nd year of life	DTaP-IPV + Priorix™ INFANRIX + IPOL + Priorix	212/181 212/181
IND studies			
213503/047 (U.S.)	4 doses INFANRIX + 3 doses of polio vaccine (either 2 IPV and 1 OPV, or 3 IPV) during the first 2 years of life, and 1 dose of MMR in 2nd year of life	DTaP-IPV + MMR_{II} INFANRIX + IPOL + MMR_{II}	200/200 200/200
213503/048 (U.S.)	4 doses INFANRIX+ 3 doses of IPV during the first 2 years of life, and 1 dose of MMR in 2nd year of life	KINRIX lot 1 + MMR_{II} KINRIX lot 2 + MMR_{II} KINRIX lot 3 + MMR_{II} INFANRIX + IPOL + MMR_{II}	1050/1053 1050/1051 1050/1052 1050/1053

N = number of subjects
OPV = oral poliovirus vaccine
MMR = measles, mumps, rubella vaccine
Priorix = GSK Biologicals' measles, mumps, rubella vaccine (not licensed in U.S.)
DTaP-IPV used in Studies 213503/046 and 213503/047 differed from KINRIX in that it also contained 2-phenoxyethanol (≤2.5 mg per dose) as a preservative.

5.3 Review Strategy

The BLA contains complete clinical study reports for Studies 213503/047 and 213503/048, and a synopsis of safety data from Study 213503/046. All of the safety and immunogenicity data provided for the pivotal study, Study 213503/048, were reviewed. All of the safety data provided for the two supportive studies were reviewed.

For Study 213503/047, the pertussis, diphtheria, and tetanus assay validation information provided in the BLA were not considered adequate by CBER product reviewers. Thus, these data were not reviewed. Because oral poliovirus vaccine (OPV) is no longer used in the U.S., the polio immunogenicity data from subjects in Study 213503/047 who received one or more doses of OPV are of limited relevance to the evaluation of KINRIX for use in U.S. children, and are not included in this review. Supportive polio immunogenicity data from the subset of subjects in Study 213503/047 who were previously primed with three doses of IPV will be presented.

5.4 Good Clinical Practices and Data Integrity

The quality of the safety and immunogenicity data in the BLA appeared to be adequate.

6 Clinical Studies

6.1 Pivotal Trial

6.1.1 Applicant's Protocol # and Protocol Title

Study 213503/048: A phase III, open (double-blind for consistency lots), randomized, single center with satellite sites, clinical trial of the safety, immunogenicity and consistency of three manufacturing lots of GSK Biologicals' DTaP-IPV candidate vaccine compared to that of separate injections of GSK Biologicals' DTaP vaccine (*Infanrix*) and Aventis Pasteur's IPV vaccine (*IPOL*) administered as booster doses to healthy children 4 to 6 years of age, each co-administered with Merck and Company's MMR vaccine (M-M-R_{II})

6.1.1.1 Objective/Rationale

The aims of the study were to demonstrate the consistency of three manufacturing lots of GSK Biologicals' KINRIX in terms of immunogenicity and to evaluate non-inferiority of KINRIX with respect to immunogenicity and limb swelling compared to the Control vaccines (separate injections of INFANRIX and IPOL) when administered as a 5th dose of DTaP and a 4th dose of IPV vaccine in subjects 4 to 6 years of age. The study also assessed the overall safety of KINRIX or Control vaccines co-administered with the second dose of MMR_{II}.

6.1.1.2 Design Overview

The study was an open (double-blind for lot consistency), randomized (1:1:1:1), multicenter study with four parallel groups: 3 lots of KINRIX and 1 Control group (INFANRIX + IPOL).

6.1.1.3 Population

Inclusion Criteria

- Child between and including 4 and 6 years of age at the time of vaccination.
- Free of obvious health problems based on medical history and evaluation.
- Received 4 doses of INFANRIX (primary vaccination course with booster dose in the second year of life) and 3 doses of IPOL during the first 2 years of life.
- Vaccination against measles, mumps, and rubella in the second year of life.
- Subjects whom the investigator believed would comply with the protocol requirements.
- Written informed consent obtained from the parent(s) or guardian(s).

Exclusion Criteria

- Use of any investigational drug or vaccine other than the study vaccines within 30 days preceding the administration of study vaccines, or planned use during the study period.
- History of previous or intercurrent diphtheria, tetanus, pertussis, polio, measles, mumps, or rubella disease, or of vaccination against these diseases given after the second year of life.
- Known exposure to diphtheria, tetanus, pertussis, or polio, prior to vaccination.
- Poliovirus vaccination with one or more doses of oral poliovirus vaccine.
- Administration or planned administration of a vaccine not foreseen by the study protocol within 30 days of study vaccination and ending at Day 30.
- Chronic administration (>14 days) or administration of immunosuppressants or other immune modifying drugs within six months prior to study vaccination or planned administration during the study period ending at Day 30. (For corticosteroids, this meant ≥0.5 mg/kg/day prednisone or equivalent for more than 14 days. Inhaled and topical steroids were allowed.)
- Administration of immunoglobulins and/or any blood products within three months prior to study vaccination or planned administration during the study period ending at Day 30.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus infection.
- History of seizures or progressive neurological disorder, including infantile spasms, uncontrolled epilepsy or progressive encephalopathy.
- Major congenital defects or serious chronic illness.
- Acute disease at the time of enrollment (warranted deferral pending recovery). (Acute disease was defined as a moderate or severe illness with or without fever. All vaccines could have been administered to persons with a minor illness such as diarrhea, mild upper respiratory infection without fever, i.e. oral/axillary temperature <99.5°F [37.5°C]).
- History of allergic disease or reactions likely to be exacerbated by any component of the vaccine(s), including allergic reactions to 2-phenoxyethanol, formaldehyde,

neomycin, polymyxin B, streptomycin, gelatin, and/or latex.
- History of anaphylactic reaction to egg proteins or previous doses of the vaccine(s).
- Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) within 7 days of administration of previous dose of INFANRIX.
- Fever ≥40.5°C or 104.9°F (rectal temperature) (39.5°C or 103.1°F, oral/axillary) within 48 hours of previous dose of INFANRIX not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of previous dose of INFANRIX.
- Persistent, severe, inconsolable screaming or crying lasting ≥3 hours which occurred within 48 hours of administration of previous dose of INFANRIX.
- Thrombocytopenia following a previous dose of MMR_{II} vaccine or its component vaccines.
- Inability to contact a parent/guardian of the subject by telephone.
- Blood dyscrasias (including current thrombocytopenia), leukemia, lymphomas or other malignant neoplasms affecting the bone marrow or lymphatic systems.
- Family history of congenital or hereditary immunodeficiency, unless the immune competence of the subject was demonstrated.

Concomitant products

All subjects received MMR_{II} concomitantly with KINRIX or Control vaccines (see Section 6.1.1.4) Concomitant administration of a U.S.-licensed influenza vaccine was allowed according to seasonal availability and investigator discretion.

The use of routine antipyretic/analgesic prophylaxis was discouraged. Parents/guardians were counseled to only use antipyretics/analgesics for treatment of post-vaccination adverse events.

6.1.1.4 Products Mandated by the Protocol

Dosage and administration of study vaccines

Subjects received a single dose of KINRIX or of INFANRIX and IPOL administered separately, co-administered at a separate site, with MMR_{II}. Concomitant administration of a U.S.-licensed influenza vaccine was allowed according to seasonal availability and at the discretion of the investigator. Table 3 presents the dosage, route, and site of administration of the study vaccines.

Table 3. Study 213503/048: Dosage and administration of study vaccines

Group	Visit	Vaccination	Dose	Route	Site	Side
KINRIX	1	KINRIX MMR_{II}	0.5 mL 0.5 mL	IM SC	Deltoid Deltoid	Upper Left Upper Right
INFANRIX+ IPOL	1	INFANRIX IPOL MMR_{II}	0.5 mL 0.5 mL 0.5 mL	IM SC SC	Deltoid Deltoid Deltoid	Upper Left Lower Right Upper Right

IM = intramuscular
SC = subcutaneous

Influenza vaccine, when administered by intramuscular injection, was given in the lower left deltoid in both groups. Intranasal influenza vaccine was also permitted.

Formulation of study vaccines

For the formulation of KINRIX, see Section 1.2.3. The lots of KINRIX used were as follows: Group 1, Lot DC20A001B; Group 2, Lot DC20A002B; Group 3, Lot DC20A003B. The bulk antigen batch numbers for the antigen concentrates that were used to formulate the KINRIX consistency lots are presented in Table 4. For each inactivated poliovirus trivalent concentrate

bulk (CPV), different monovalent (Type 1, Type 2 and Type 3) poliovirus bulks were used (BLA 125260/0.0, m3.2.S.4.4, batch-analysis.pdf, page 4). Each of the Diphtheria and Tetanus Toxoids Adsorbed Combined Bulk (DT conc) contained different lots of purified diphtheria and tetanus toxoids (BLA STN 103648/5046; Dr. Theresa Finn review memo).

Table 4. Study 213503/048 KINRIX clinical lots

[ ]

DT conc = Diphtheria and Tetanus Toxoids Adsorbed Combined Bulk
CPV = inactivated poliovirus trivalent concentrate bulk
Source: BLA 125260/0.0, m3.2.P.5.4, batch-analyses.pdf, page 4

The formulation of INFANRIX used in this study, per 0.5 ml dose is as follows:
Diphtheria toxoid 25 Lf
Tetanus toxoid 10 Lf
PT 25 µg
FHA 25 µg
PRN 8 µg
Aluminum as salts 0.5 mg
2-phenoxyethanol ≤2.5 mg

The formulation of IPOL per 0.5 ml dose is as follows:
Poliovirus type 1 (Mahoney) 40 D-Antigen units
Poliovirus type 2 (MEF-1) 8 D-Antigen units
Poliovirus type 3 (Saukett) 32 D-Antigen units
2-phenoxyethanol 0.5%
formaldehyde <0.02%

The formulation of MMR_{II} per 0.5 ml dose is as follows:
Measles virus ≥1,000 TCID50 (tissue culture infectious doses)
Mumps virus 20,000 TCID50
Rubella virus 1,000 TCID50

6.1.1.5 Endpoints

6.1.1.5.1 Primary Immunogenicity Endpoints

Lot consistency (one month post-vaccination)

The three KINRIX lots would be considered consistent, if, for each antigen (D, T, PT, FHA, PRN, and Poliovirus types 1, 2, and 3), and each pair wise comparison between lots, the 95% CIs of the GMC or GMT ratios are included within the interval [0.67,1.5].

Non-inferiority of KINRIX relative to INFANRIX + IPOL (one month post-vaccination)

The primary non-inferiority immunogenicity endpoints and evaluation criteria are presented in Table 5.

Table 5. Study 213503/048: Primary non-inferiority immunogenicity endpoints and evaluation criteria

Antibody	Endpoint (one month after vaccination)	Non-inferiority criterion
anti-diphtheria toxoid anti-tetanus toxoid	percent of subjects with booster response: • initially seronegative (<0.1 IU/ml): ≥0.4 IU/ml • initially seropositive (≥0.1 IU/ml): ≥4-times pre-vaccination level	upper limit of 95% CI for difference [(INFANRIX + IPOL) minus $KINRIX_{pooled\ lots}$] ≤10%
anti-PT, FHA, PRN	percent of subjects with booster response: • initially seronegative (<5 EU/ml): ≥20 EU/ml • initially seropositive ≥5 EU/ml and <20 EU/ml: ≥4-times pre-vaccination level • initially seropositive ≥20 EU/ml: ≥2-times pre-vaccination level	upper limit of 95% CI for difference [(INFANRIX + IPOL) minus $KINRIX_{pooled\ lots}$) ≤10%
anti-polio 1, 2, 3	GMTs	upper limit of 95% CI for GMT ratio (INFANRIX + IPOL over $KINRIX_{pooled\ lots}$) ≤1.5

6.1.1.5.2 Secondary Immunogenicity Endpoints

Selected secondary immunogenicity endpoints are presented in Table 6.

Table 6. Study 213503/048: Selected secondary immunogenicity endpoints

Antibody	Endpoint (one month after vaccination)
anti-diphtheria toxoid	• % ≥0.1 IU/ml • % ≥1.0 IU/ml • GMC
anti-tetanus toxoid	• % ≥0.1 IU/ml • % ≥1.0 IU/ml • GMC
anti-PT, FHA, PRN	• GMC
anti-polio types 1, 2, 3	• booster response: o initially seronegative (<1:8): post-vaccination titer ≥1:32 o initially seropositive (≥1:8): ≥4-times pre-titer • % with post-vaccination titer ≥1:8

6.1.1.5.3 Primary Safety Endpoint

The incidence of increased circumferential swelling at the DTaP-containing vaccine injection site within 4 days (Day 0 through Day 3) after vaccination was a primary safety endpoint. Increased circumferential swelling was defined as an injection site swelling diameter that involves >50% of the length of the upper arm that also is associated with a >30 mm increase of the mid-upper arm circumference compared to the baseline measurement. KINRIX would be considered non-inferior to separately administered INFANRIX + IPOL with regard to increased circumferential swelling at the DTaP-based injection site if the upper limit of the two-sided 95% CI for the difference ($KINRIX_{pooled\ lots}$ minus Control) in the percentage of subjects with the event was 2% or less.

6.1.1.5.4 Secondary Safety Endpoints

- Incidence of solicited local (pain, redness, and swelling) and general (fever, drowsiness, and loss of appetite) symptoms within 4 days (Day 0 through Day 3) after vaccination
- Increase in the mid-upper arm circumference at the DTaP-containing vaccine injection site within 4 days (Day 0 through Day 3) after vaccination

- Incidence of general symptoms that may be associated with MMR vaccination (fever, rash/exanthem, parotid/salivary gland swelling, and any suspected signs of meningism including febrile convulsions) within 15 days (Day 0 through Day 14) after vaccination
- Incidence of unsolicited symptoms within 31 days (Day 0 through Day 30) after vaccination
- Occurrence during the entire study period (from Visit 1 through 6 months [minimum 182 days] post-vaccination) of serious adverse events
- Occurrence during the extended safety follow-up phase (from Day 31 through 6 months [minimum 182 days] post-vaccination) of:
  - onset of chronic illness(es) (e.g., type I diabetes, autoimmune diseases, asthma, and allergies)
  - adverse events leading to emergency room visits or to physician office visits that are not related to well-child care, vaccination, injury or common acute illnesses such as upper respiratory tract infection, otitis media, pharyngitis, and gastroenteritis

6.1.1.6 Surveillance/Monitoring

6.1.1.6.1 Immunogenicity Monitoring

A subset of subjects, equally distributed between the four treatment groups (i.e., three KINRIX lots and Control group), provided blood samples for serological analysis prior to vaccination and 31-48 days post-vaccination. This subset was referred to as the safety and immunogenicity subset and was planned to consist of the first 1,340 vaccinated subjects who agreed to be part of the subset. In case of insufficient blood sample volume to perform all assays, the assays for KINRIX antigens were prioritized as follows: polio type 1, polio type 2, polio type 3, PT, FHA, PRN, diphtheria, tetanus.

Serological assays performed for this study are listed in Table 7.

Table 7. Study 213503/048 Serological assays for KINRIX antigens

Marker	Assay method	Assay unit	Assay cut-off	Laboratory
anti-diphtheria toxoid	ELISA	IU/mL	0.1	GSK Rixensart
anti-tetanus toxoid	ELISA	IU/mL	0.1	GSK Rixensart
anti-PT	ELISA	EU/mL	5	GSK Rixensart
anti-FHA	ELISA	EU/mL	5	GSK Rixensart
anti-PRN	ELISA	EU/mL	5	GSK Rixensart
anti-poliovirus types 1, 2, 3	Neutralization	ED50	1:8	GSK Rixensart

6.1.1.6.2 Safety Surveillance/Monitoring

- Prior to vaccination at the first study visit, study personnel measured and recorded the length of subjects' both upper arms (from acromion to tip of elbow) and the mid-upper arm circumference (at mid-distance between the acromion and the tip of the elbow, while the arm was held parallel to the trunk and the elbow was flexed in front at 90^{o}) of both arms. The arms were marked at the site of measurement of the circumference.
- Memory aids were used to record daily the occurrence and severity of any pain, redness, or swelling at each injection site, mid-upper arm circumference bilaterally, drowsiness, and loss of appetite on Days 0-3 post-vaccination. Oral temperatures were recorded daily on Days 0-14 post-vaccination.
- Memory aids were not collected. Information from the memory aids on solicited local and systemic reactions that occurred on Days 0-3 post-vaccination was obtained during follow-up telephone calls conducted on Day 4-6 post-vaccination for all subjects. Telephone follow-up to inquire about adverse events was also conducted on Day 31-38 post-vaccination for

subjects not in the immunogenicity subset, and on Day 182-194 post-vaccination for all subjects.

- If during Days 0-3 post-vaccination, parents/guardians observed/measured injection site swelling >50 mm, an increase of >30 mm in mid-upper arm circumference compared to pre-vaccination, or any swelling that interfered with usual activities, they were to contact study personnel and take the subject to the investigator's site for evaluation as soon as possible. The investigator was to complete a standardized swelling assessment form that captured information on the extent of the swelling, the presence of induration, the presence of pruritis, and functional impairment. For subjects who did not come to the study site for evaluation, the information requested on the standardized swelling form was obtained by telephone follow-up.
- Parents/guardians were to contact the study site for symptoms that may be associated with MMR (rashes/exanthem, parotid/salivary gland swelling, signs of meningismus, including febrile seizure) that occurred anytime on Days 0-14 post-vaccination.
- Unsolicited adverse events were monitored for a minimum of 31 days following vaccination.
- Serious adverse events were monitored through 6 months after vaccination.
- Onset of chronic illness, emergency room visits, and physician office visits not related to well-child care, vaccination, or common acute illnesses were monitored from ~30 days through 6 months post-vaccination.
- With the exception of events that were to trigger contact with study personnel according to the protocol, the subject's parent/guardian were asked if they sought medical advice (hospitalization, emergency room visit or a visit to or from medical personnel [M.D., D.O., or nurse practitioner]) for solicited and unsolicited symptoms.

6.1.1.7 Statistical Considerations

6.1.1.7.1 Sample Size/Statistical Power

A total of 4,200 subjects were planned to be enrolled and randomized to receive either one of three lots of KINRIX or Control vaccines (INFANRIX + IPOL) in a 1:1:1:1 ratio. Allowing for approximately 5% of subjects who may not be evaluable for analysis and assuming an expected incidence of 1.5%, the power to detect a 2.0% increase in the incidence of increased circumferential swelling (diameter of swelling involving >50% of the length of the upper arm associated with >30 mm increase over baseline circumference) at the KINRIX vs. INFANRIX injection site was >90%.

For the primary immunogenicity analyses, 1,200 evaluable subjects (300 in each group) were sufficient. Allowing for up to 10% of non-evaluable subjects, blood was obtained from 1,340 subjects (335 in each group).

For each of the lot consistency analyses, the statistical power was estimated as >90%, with an overall power of at least 88% for all of the lot consistency analyses.

The global power to conclude non-inferiority of KINRIX relative to INFANRIX + IPOL for all the antigens was estimated to be 99.9%.

6.1.1.7.2 Study Cohorts Analyzed

Total Vaccinated Cohort

The Total Vaccinated Cohort for safety included all subjects vaccinated. This was the primary cohort for the analysis of safety.

The Total Vaccinated Cohort for immunogenicity included all vaccinated subjects for whom data concerning immunogenicity endpoint measures were available.

The Total Vaccinated Cohort analyses were performed per vaccine actually injected.

According-To-Protocol (ATP) Cohort for Safety
The ATP cohort for analysis of safety included all subjects who:
- received study vaccines according to protocol
- did not receive a vaccine forbidden in the protocol
- received three doses of IPV and four doses of INFANRIX in the first two years of life.

If 5% or more of the Total Vaccinated subjects were excluded from the ATP Cohort for Safety, a second analysis would be performed on the ATP Cohort for Safety.

According To Protocol (ATP) Cohort for Immunogenicity
The ATP Cohort for Immunogenicity included all evaluable subjects (i.e., those meeting eligibility criteria, complying with protocol procedures, with no elimination criteria during the study) from the ATP Cohort for Safety for whom data concerning immunogenicity endpoint measures were available. This cohort included subjects for whom assay results were available for antibodies against at least one study vaccine antigen after vaccination. The interval between vaccination and the post-vaccination blood draw for inclusion in the ATP Cohort for Immunogenicity was defined as 31 to 48 days.

The primary immunogenicity analyses were based on the ATP Cohort for Immunogenicity. If the percentage of Total Vaccinated subjects excluded from the ATP Cohort for Immunogenicity was more than 5%, the protocol specified that a second analysis of immunogenicity based on the Total Vaccinated Cohort would be performed.

Extended Safety Follow-up (ESFU) Cohort
The ESFU Cohort included all vaccinated subjects who had a follow-up contact during the ESFU period (i.e., from Day 31 to 6 months post-vaccination) or who had the onset of a chronic illness, unsolicited adverse event, or a serious adverse event beyond 30 days after vaccination.

6.1.1.7.3 Statistical Analyses
Equivalency criteria for KINRIX lot comparisons were provided in Section 6.1.1.5.1. The 95% confidence intervals for the GMC/GMT ratios were derived using an ANCOVA model on the three consistency lots. The model included the log of the pre-vaccination concentration/titer as regressor and assumed common variance on the three lots.

Non-inferiority criteria for the primary immunogenicity and safety analyses were provided in Sections 6.1.1.5.1 and 6.1.1.5.2, respectively. For the non-inferiority analyses of anti-poliovirus GMTs, the 95% confidence intervals for the GMT ratios were derived using an ANCOVA model on the two groups. The model included the log of the pre-vaccination titer as regressor and assumed common variance on the two groups.

For exploratory safety analyses between groups, a p-value below 0.05 was used to identify potential differences between groups.

6.1.2 Results

6.1.2.1 Populations Enrolled/Analyzed

6.1.2.1.1 Study Sites and Study Period

Twenty four study centers enrolled a total of 4,209 subjects. Enrollment, by center, ranged from 9 to 394 subjects. Nine centers had an enrollment of ≥5 percent of the total subjects and 15 centers had an enrollment of less than 5 percent of the total subjects.

The first subject was enrolled in the study on 1/5/05. The last active phase study visit was on 7/06/06. The last ESFU contact was on 12/13/06.

6.1.2.1.2 Subject Disposition and Follow-up

Table 8 and Table 9 present the number of subjects vaccinated, completed, and withdrawn by group (KINRIX pooled and Control) and reason in the active phase and the ESFU phase, respectively.

Table 8. Study 213503/048 Subjects vaccinated, completed, withdrawn and reason for withdrawal for the Active Phase (Total Vaccinated Cohort)

	Pooled KINRIX	INFANRIX + IPOL	Total
Number of subjects vaccinated	3156	1053	4209
Number of subjects completed	3094	1029	4123
Number of subjects withdrawn	62	24	86
Reasons for withdrawal:			
Adverse Event	0	0	0
Protocol violation	0	0	0
Consent withdrawal (not due to an adverse event)	2	0	2
Migrated/moved from study area	0	0	0
Lost to follow-up	59	22	81
Others	1	2	3[1]

[1]Two subjects discontinued healthcare at study site. One subject did not accept telephone calls.
Vaccinated = number of subjects who where vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come for the last visit
Note: One subject without visit 2 was treated as a completer. One subject with a visit 2 date was treated as a drop-out because of loss of insurance coverage during the study**.** Safety data post-vaccination was recorded for the subject.
Source: 125260/0.1, m5.3.5.1.3, 048-report-body.pdf, page 77

Table 9. Study 213503/048 Counts of subjects vaccinated, completed, withdrawn and reason for withdrawal for the ESFU Phase (Total Vaccinated Cohort)

	Pooled KINRIX	INFANRIX + IPOL	Total
Number of subjects enrolled and vaccinated	3156	1053	4209
Number of vaccinated subjects in ESFU cohort	3071	1022	4093
Number of subjects withdrawn from ESFU Phase	85	31	116
Reasons for withdrawal:			
Consent withdrawal (not due to an adverse event)	1	0	1
Lost to follow-up	84	31	115

Vaccinated = number of subjects who where vaccinated in the study
Withdrawn = number of subjects not contacted for the concluding contact
Source: 125260/0.1, m5.3.5.1.3, 048-report-body.pdf, page 78

Table 10 presents a summary of the subjects enrolled and included in the safety analyses as well as those excluded from the safety analyses and the reason for elimination. Seven subjects (3 in the KINRIX group and 4 in the INFANRIX + IPOL group) were excluded from the ATP Cohort for Safety due to study vaccine not administered according to protocol. Three of these subjects received an additional dose of IPOL and four subjects did not receive a dose of IPOL. Twenty three subjects (15 in the KINRIX group and 8 in the INFANRIX + IPOL group) were excluded from the ATP Cohort for Safety due to vaccination history non-compliant with protocol.

Because the percentage of the Total Vaccinated Cohort excluded from the ATP Cohort for Safety was <5%, a separate analysis of the ATP Cohort for Safety was not done. All safety analyses were conducted with the Total Vaccinated Cohort.

Table 10. Study 213503/048 Subjects enrolled/randomized into the Active Phase of the study and excluded from the ATP Cohort for Safety and ESFU Cohort with reasons for exclusions

	Total			Pooled KINRIX		INFANRIX + IPOL	
	n	s	%	n	s	n	s
Active Phase							
Total enrolled Cohort	4209						
Total Vaccinated Cohort	4209		100	3156		1053	
Study vaccine not administered according to protocol (code 1070)	7	7		3	3	4	4
Others (vaccination history) (code 1500)	23	23		15	15	8	8
ATP Cohort for Safety	4179		99.3	3138		1041	
ESFU Phase							
Total Vaccinated Cohort	4209		100	3156		1053	
No safety follow-up contact and did not report an adverse event after Day 30 (code 3000)	116	116		85	85	31	31
ESFU Cohort	4093		97.2	3071		1022	

Percent = percentage of subjects in the considered ATP Cohort relative to the Total Vaccinated Cohort.
Subjects may have more than one elimination code assigned. Therefore, for each elimination reason, n and s is provided where:
n= number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s= number of subjects with the elimination code assigned
Codes are listed based on a ranking order
Code 1500 (vaccination history) = subjects who did not receive 3 doses of IPV and 4 doses of INFANRIX in the first 2 years of life
Source: 125260/0.1, m5.3.5.1.3, 048-report-body.pdf, page 79

Table 11 presents a summary of the subjects enrolled and included in the analyses, as well as those excluded from the analyses and the reason for elimination for the immunogenicity and safety subset. Because the proportion of subjects excluded from the Total Vaccinated Cohort and the ATP Cohort for Immunogenicity was >5%, an analysis of the Total Vaccinated Cohort was conducted to complement the ATP immunogenicity analysis.

Table 11. Study 213503/048 Subjects enrolled/randomized into the Active Phase of the study and excluded from the ATP Cohort for Safety and ATP Cohort for Immunogenicity with reasons for exclusions, immunogenicity and safety subset

	Total			KINRIX Lot 1		KINRIX Lot 2		KINRIX Lot 3		Pooled KINRIX		INFANRIX + IPOL	
	n	s	%	n	s	n	s	n	s	n	s	n	s
Total enrolled cohort	1331												
Total vaccinated cohort	1331		100	334		331		332		997		334	
Study vaccine dose not administered according to protocol (code 1070)	2	2		0	0	1	1	0	0	1	1	1	1
Others (vaccination history) (code 1500)	8	8		2	2	2	2	1	1	5	5	3	3
ATP safety cohort	1321		99.2	332		328		331		991		330	
Protocol violation (inclusion/exclusion criteria) (code 2010)	0	1		0	0	0	0	0	1	0	1	0	0
Initially unknown antibody status (code 2020)	5	5		0	0	1	1	1	1	2	2	3	3
Non-compliance with blood sampling schedule including wrong and unknown dates (code 2090)	66	66		20	20	11	11	16	16	47	47	19	19
Essential serological data missing (code 2100)	135	142		27	28	33	33	29	30	89	91	46	51
ATP immunogenicity cohort	1115		83.8	285		283		285		853		262	

Percent = percentage of subjects in the considered ATP Cohort relative to the Total Vaccinated Cohort.
Subjects may have more than one elimination code assigned therefore for each elimination reason n and s is provided where:
n= number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s= number of subjects with the elimination code assigned
Codes are listed based on a ranking order
Code 1500 (vaccination history) = subjects who did not receive 3 doses of IPV vaccine and 4 doses of INFANRIX in the first 2 years of life
Source: 125260/0.1, m5.3.5.1.3, 048-report-body.pdf, page 80

Table 12 and Table 13 present the number and percentage of subjects who received influenza vaccine for the Total Vaccinated Cohort and the Total Vaccinated Cohort Immunogenicity and Safety Subset, respectively.

Table 12. Study 213503/048 Number and percentage of subjects who received influenza vaccine, Total Vaccinated Cohort

Pooled KINRIX N = 3156		INFANRIX + IPOL N = 1053		Total N = 4209	
n	%	n	%	n	%
126	4.0	51	4.8	177	4.2

Source: 125260/0.1, m5.3.5.1.3, 048-report-body.pdf, page 135

Table 13. Study 213503/048 Number and percentage of subjects who received influenza vaccine, Total Vaccinated Cohort Immunogenicity and Safety Subset

Pooled KINRIX N = 997		INFANRIX + IPOL N = 334		Total N = 1331	
n	%	n	%	n	%
5	0.5	11	3.3	16	1.2

Source: 125260/0.1, m5.3.5.1.3, 048-report-body.pdf, page 136

6.1.2.1.3 Subject Demographics

Table 14 summarizes demographic characteristics of subjects included in the Total Vaccinated Cohort for the KINRIX groups pooled and the INFANRIX + IPOL group. The three KINRIX groups were similar with regard to age, gender, and racial characteristics. The Total Vaccinated Cohort and the ATP Cohort for Immunogenicity were similar to each other with regards to age, gender, and racial characteristics.

Table 14. Study 213503/048 Summary of demographic characteristics, Total Vaccinated Cohort

		Pooled KINRIX N = 3156		INFANRIX + IPOL N = 1053		Total N = 4209	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Age (years)	Mean	4.2		4.2	-	4.2	-
	SD	0.37		0.38	-	0.37	-
	Median	4.0		4.0	-	4.0	-
	Minimum	4		4	-	4	-
	Maximum	6		6	-	6	-
Gender	Female	1574	49.9	513	48.7	2087	49.6
	Male	1582	50.1	540	51.3	2122	50.4
Race	Black	216	6.8	77	7.3	293	7.0
	White/ Caucasian	1463	46.4	457	43.4	1920	45.6
	Oriental	0	0.0	0	0.0	0	0.0
	Arabic/north African	20	0.6	10	0.9	30	0.7
	East/south east Asian	253	8.0	103	9.8	356	8.5
	South Asian	151	4.8	50	4.7	201	4.8
	American Hispanic	597	18.9	194	18.4	791	18.8
	Japanese	11	0.3	4	0.4	15	0.4
	Other	445	14.1	158	15.0	603	14.3

SD= standard deviation

Source: 125260/0.1, m5.3.5.1.3, 048-report-body.pdf, page 82

6.1.2.1.4 Use of Antipyretics

Table 15 presents the percentage of subjects who received antipyretics during the 4-day and 15-day follow-up periods after vaccination.

Table 15. Study 213503/048 Use of antipyretics (Day 0-3 and Day 0-14) (Total vaccinated cohort)

	Pooled KINRIX					INFANRIX + IPOL				
				95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL
Day 0 –Day 3										
Any antipyretic	3156	1084	34.3	32.7	36.0	1053	337	32.0	29.2	34.9
Prophylactic antipyretic	3156	317	10.0	9.0	11.1	1053	89	8.5	6.8	10.3
Day 0- Day 14										
Any antipyretic	3156	1197	37.9	36.2	39.6	1053	375	35.6	32.7	38.6
Prophylactic antipyretic	3156	319	10.1	9.1	11.2	1053	89	8.5	6.8	10.3

N =number of subjects having received at least one dose
n/% = number/percentage of subjects who started to take the specified concomitant medication at least once during the specified period
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Source: 125260/0.1, m5.3.5.1.3, 048-report-body.pdf, page 120

6.1.2.2 Immunogenicity Outcomes

6.1.2.2.1 Consistency of Manufacturing Lots of KINRIX

Table 16 presents the ratios of post-vaccination antibody GMCs or GMTs between pairs of KINRIX lots for each vaccine antigen for the ATP Cohort for Immunogenicity. For each pair of lots and for each vaccine antigen, the lower and upper limits of the 95% CIs for the GMC or GMT ratios were within the pre-defined clinical limits of (0.67, 1.5). For the complementary analyses for the Total Vaccinated Cohort, all consistency criteria were also met.

Table 16. Study 213503/048 Ratios of post-vaccination antibody GMCs or GMTs (adjusted for baseline concentration) between KINRIX lots one month after vaccination (ATP Cohort for Immunogenicity)

KINRIX Lot A	N	Adjusted GMC or GMT	KINRIX Lot B	N	Adjusted GMC or GMT	GMC or GMT Ratio			Consistency criterion met (Yes/No)
						Lot A/ Lot B	95% CI		
							LL	UL	
Anti-Diphtheria Toxoid (IU/mL)									
Lot 1	280	17.460	Lot 2	282	17.996	0.970	0.871	1.080	Yes
Lot 1	280	17.460	Lot 3	282	18.161	0.961	0.863	1.070	Yes
Lot 2	282	17.996	Lot 3	282	18.161	0.991	0.890	1.103	Yes
Anti-Tetanus Toxoid (IU/mL)									
Lot 1	279	9.796	Lot 2	283	10.050	0.975	0.866	1.097	Yes
Lot 1	279	9.796	Lot 3	282	11.160	0.878	0.780	0.988	Yes
Lot 2	283	10.050	Lot 3	282	11.160	0.901	0.800	1.014	Yes
Anti-PT (EU/mL)									
Lot 1	272	67.9	Lot 2	273	72.4	0.938	0.828	1.063	Yes
Lot 1	272	67.9	Lot 3	277	70.5	0.963	0.850	1.091	Yes
Lot 2	273	72.4	Lot 3	277	70.5	1.026	0.906	1.162	Yes
Anti-FHA (EU/mL)									
Lot 1	281	814.7	Lot 2	280	932.2	0.874	0.783	0.976	Yes
Lot 1	281	814.7	Lot 3	283	860.3	0.947	0.849	1.057	Yes
Lot 2	280	932.2	Lot 3	283	860.3	1.084	0.971	1.209	Yes
Anti-PRN (EU/mL)									
Lot 1	280	606.8	Lot 2	281	608.0	0.998	0.867	1.148	Yes
Lot 1	280	606.8	Lot 3	284	581.8	1.043	0.907	1.200	Yes
Lot 2	281	608.0	Lot 3	284	581.8	1.045	0.909	1.202	Yes
Anti-poliovirus type 1									
Lot 1	270	2113.5	Lot 2	266	2126.8	0.994	0.836	1.181	Yes
Lot 1	270	2113.5	Lot 3	273	2142.3	0.987	0.831	1.172	Yes
Lot 2	266	2126.8	Lot 3	273	2142.3	0.993	0.836	1.180	Yes
Anti-poliovirus type 2									
Lot 1	274	2361.8	Lot 2	268	2112.9	1.118	0.951	1.314	Yes
Lot 1	274	2361.8	Lot 3	265	2346.7	1.006	0.856	1.183	Yes
Lot 2	268	2112.9	Lot 3	265	2346.7	0.900	0.765	1.060	Yes
Anti-poliovirus type 3									
Lot 1	269	3754.6	Lot 2	255	3376.7	1.112	0.941	1.314	Yes
Lot 1	269	3754.6	Lot 3	263	3631.4	1.034	0.876	1.220	Yes
Lot 2	255	3376.7	Lot 3	263	3631.4	0.930	0.787	1.099	Yes

Adjusted GMC (GMT) = geometric mean antibody concentration (titer) adjusted for baseline concentration (titer)
N = Number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMC (GMT) ratio (ANCOVA model: adjustment for baseline concentration (titer) - pooled variance with more than 2 groups)
LL = lower limit, UL = upper limit
Criteria for claiming lot-to-lot consistency - 95% CI for the point estimate of the between-lot GMC (GMT) ratio completely within the range (0.67, 1.5)
Source: 125260/0.1, m5.3.5.1.3, 048-report-body.pdf, page 92

6.1.2.2.2 Non-inferiority of KINRIX Relative to INFANRIX + IPOL

Table 17 presents the proportions of subjects with diphtheria and tetanus booster responses according to seropositivity status at baseline.

Table 17. Study 213503/048 Percentage of subjects with booster responses for Anti-Diphtheria Toxoid and Anti-Tetanus Toxoid antibodies one month after vaccination (ATP Cohort for Immunogenicity)

				Booster Response			
						95% CI	
Antibody	Group	Pre-vaccination status	N	n	%	LL	UL
Anti-Diphtheria Toxoid	Pooled KINRIX	S-	104	104	100	-	-
		S+	740	736	99.5	-	-
		Total	844	840	99.5	98.8	99.9
	INFANRIX + IPOL	S-	37	37	100	-	-
		S+	223	223	100	-	-
		Total	260	260	100	98.6	100
Anti-Tetanus Toxoid	Pooled KINRIX	S-	103	102	99.0	-	-
		S+	741	714	96.4	-	-
		Total	844	816	96.7	95.2	97.8
	INFANRIX + IPOL	S-	31	31	100	-	-
		S+	230	214	93.0	-	-
		Total	261	245	93.9	90.2	96.5

S+ = subjects with concentrations ≥ 0.1 IU/mL
S- = subjects with concentrations < 0.1 IU/mL
Total = subjects either seropositive or seronegative at pre-vaccination
N = number of subjects with available results at PRE and POST time point
n/% = number/percentage of subjects with a booster response
95% CI = exact 95% confidence interval; LL = Lower Limit; UL = Upper Limit
Booster response defined as:
For initially seronegative subjects, antibody concentration >= 0.4 IU/mL one month post-vaccination
For initially seropositive subjects, antibody concentration one month post-vaccination >= 4 fold the pre-vaccination antibody concentration
Source: 125260/0.1, m5.3.5.1.3, 048-report-body.pdf, page 95

Table 18 presents the proportions of subjects with booster responses for pertussis antigens according to seropositivity status at baseline.

Table 18. Study 213503/048 Percentage of subjects with booster responses for Anti-PT, Anti-FHA, Anti-PRN antibodies one month after vaccination (ATP Cohort for Immunogenicity)

				Booster Response			
						95% CI	
Antibody	Group	Pre-vaccination status	N	n	%	LL	UL
Anti-PT	Pooled KINRIX	S-	566	520	91.9	-	-
		S+ (<20 EU/mL)	217	207	95.4	-	-
		S+ (≥20 EU/mL)	39	31	79.5	-	-
		Total	822	758	92.2	90.2	94.0
	INFANRIX + IPOL	S-	167	152	91.0	-	-
		S+ (<20 EU/mL)	73	71	97.3	-	-
		S+ (≥20 EU/mL)	16	14	87.5	-	-
		Total	256	237	92.6	88.7	95.5
Anti-FHA	Pooled KINRIX	S-	14	14	100	-	-
		S+ (<20 EU/mL)	186	186	100	-	-
		S+ (≥20 EU/mL)	644	605	93.9	-	-
		Total	844	805	95.4	93.7	96.7
	INFANRIX + IPOL	S-	4	4	100	-	-
		S+ (<20 EU/mL)	56	56	100	-	-
		S+ (≥20 EU/mL)	201	191	95.0	-	-
		Total	261	251	96.2	93.1	98.1
Anti-PRN	Pooled KINRIX	S-	74	73	98.6	-	-
		S+ (<20 EU/mL)	229	227	99.1	-	-
		S+ (≥20 EU/mL)	542	526	97.0	-	-
		Total	845	826	97.8	96.5	98.6
	INFANRIX + IPOL	S-	25	23	92.0	-	-
		S+ (<20 EU/mL)	68	68	100	-	-
		S+ (≥20 EU/mL)	168	162	96.4	-	-
		Total	261	253	96.9	94.1	98.7

S+ = subjects with titers ≥5 EU/mL
S- = subjects with titers <5 EU/mL
N = number of subjects with available results at PRE and POST time point
n/% = number/percentage of subjects with a booster response
95% CI = exact 95% confidence interval; LL = Lower Limit; UL = Upper Limit
Total = subjects either seropositive or seronegative at pre-vaccination
Booster response defined as:
For initially seronegative subjects, antibody concentration ≥20 EU/mL one month post-vaccination
For initially seropositive subjects with pre-vaccination antibody concentration <20 EU/mL: antibody concentration one month post-vaccination ≥4 fold the pre-vaccination antibody concentration
For initially seropositive subjects with pre-vaccination antibody concentration ≥20 EU/mL: antibody concentration one month post-vaccination ≥2 fold the pre-vaccination antibody concentration
Source: 125260/0.1, m5.3.5.1.3, 048-report-body.pdf, page 98

Table 19 presents the primary non-inferiority analyses with respect to booster response rates for diphtheria, tetanus, and pertussis antigens.

Table 19. Study 213503/048 Difference between groups in percentage of subjects in the pooled KINRIX and INFANRIX + IPOL groups with a booster response to DTaP antigens one month after vaccination (ATP Cohort for Immunogenicity)

Antibody	Pooled KINRIX			INFANRIX + IPOL			Difference (INFANRIX + IPOL minus pooled KINRIX) (%)	95% CI		Non-inferiority criterion met (Yes/No)
	N	n	%	N	n	%		LL	UL	
Anti-D	844	840	99.5	260	260	100	0.47	-0.98	1.21	Yes
Anti-T	844	816	96.7	261	245	93.9	-2.81	-6.55	-0.09	Yes
Anti-PT	822	758	92.2	256	237	92.6	0.36	-3.83	3.71	Yes
Anti-FHA	844	805	95.4	261	251	96.2	0.79	-2.50	3.21	Yes
Anti-PRN	845	826	97.8	261	253	96.9	-0.82	-3.79	1.14	Yes

N = Total number of subjects with available results at PRE and POST timepoint.
n/% = number/ percentage of subjects with a booster response at post-vaccination.
95% CI, LL/UL = Standardized asymptotic 95% confidence interval around difference, Lower/Upper limit.
D = Diphtheria Toxoid
T = Tetanus Toxoid
Non-inferiority criterion: UL of the 95% CI for the point estimate of the difference between groups in percentage of subjects with a booster response is 10% or less.
See Tables 17 and 18 and Section 6.1.1.5.1 for definitions of booster response.
Source: 125260/0.1, m5.3.5.1.3, 048-report-body.pdf, page 102

Results of analyses of between group differences in the percentage of subjects with a booster response for anti-diphtheria toxoid, anti-tetanus toxoid, anti-FHA, anti-PRN, and anti-PT antibody one month post-vaccination using the Total Vaccinated Cohort were similar to those obtained for the ATP Cohort for Immunogenicity. Using the Total Vaccinated Cohort, for each of these analyses, the pre-specified non-inferiority criterion for booster response rate also would have been met.

Table 20 presents the primary non-inferiority analyses with respect to post-vaccination anti-poliovirus antibody GMTs.

Table 20. Study 213503/048 Adjusted ratios of anti-poliovirus types 1, 2, and 3 GMTs between the pooled KINRIX and INFANRIX + IPOL groups, one month after vaccination (ATP Cohort for Immunogenicity)

Antibody	Pooled KINRIX		INFANRIX + IPOL		Adjusted GMT ratio (INFANRIX + IPOL/ pooled KINRIX)	95% CI		Non-inferiority criterion met (Yes/No)
	N	Adjusted GMT	N	Adjusted GMT		LL	UL	
Anti-poliovirus type 1	809	2127.0	249	1684.6	0.792	0.680	0.922	Yes
Anti- poliovirus type 2	807	2265.2	252	1817.7	0.802	0.696	0.925	Yes
Anti- poliovirus type 3	787	3588.1	237	3365.1	0.938	0.811	1.085	Yes

N = Total number of subjects with available results at PRE and POST timepoint.
Adjusted GMT = geometric mean antibody titer adjusted for baseline titer
95% CI, LL/UL = 95% confidence interval for the adjusted GMT ratio (ANCOVA model: adjustment for baseline titer – pooled variance), Lower/Upper limit.
Criteria for claiming non-inferiority – upper limit of the 95% CI for the point estimate of the between-group GMT ratio is 1.5 or less
Source: 125260/0.1, m5.3.5.1.3, 048-report-body.pdf, page 102

Results of analyses of ratios of post-vaccination anti-poliovirus GMTs in the pooled KINRIX and INFANRIX + IPOL groups using the Total Vaccinated Cohort were similar to those obtained for the ATP Cohort for Immunogenicity. Using the Total Vaccinated cohort, for each poliovirus type, the pre-specified non-inferiority criterion also would have been met.

6.1.2.2.3 Selected Secondary and Exploratory Analyses

Table 21 presents analyses of diphtheria and tetanus seroprotection rates and GMCs before and one month post-vaccination.

Table 21. Study 213503/048 Percentage of subjects with anti-Diphtheria Toxoid and anti-Tetanus Toxoid antibody concentrations of at least 0.1 IU/mL, and at least 1.0 IU/mL and GMCs before and one month after vaccination (ATP Cohort for Immunogenicity)

				≥**0.1 IU/mL**				≥**1.0 IU/mL**				GMC (IU/mL)		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
Anti-D	Pooled KINRIX	PRE	847	743	87.7	85.3	89.9	77	9.1	7.2	11.2	0.295	0.277	0.315
		PI(M1)	850	850	100	99.6	100	850	100	99.6	100	17.910	16.973	18.898
	INFANRIX + IPOL	PRE	262	224	85.5	80.6	89.5	25	9.5	6.3	13.8	0.282	0.249	0.320
		PI(M1)	260	260	100	98.6	100	260	100	98.6	100	18.112	16.443	19.949
Anti-T	Pooled KINRIX	PRE	846	743	87.8	85.4	90.0	130	15.4	13.0	18.0	0.353	0.326	0.381
		PI(M1)	851	851	100	99.6	100	844	99.2	98.3	99.7	10.299	9.764	10.864
	INFANRIX + IPOL	PRE	262	231	88.2	83.6	91.8	64	24.4	19.3	30.1	0.404	0.346	0.472
		PI(M1)	261	261	100	98.6	100	261	100	98.6	100	11.235	10.275	12.284

GMC = geometric mean antibody concentration
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
D = Diphtheria Toxoid
T = Tetanus Toxoid
PRE =pre-vaccination blood sample at Day 0
PI(M1) =post-vaccination blood sample at Month 1
Source: 125260/0.1, m5.3.5.1.3, 048-report-body.pdf, page 94

Table 22 presents analyses of pertussis antibody GMCs at baseline and one month post-vaccination.

Table 22. Study 213503/048 Pertussis antibody GMCs before and one month after vaccination (ATP Cohort for Immunogenicity)

				GMC	95% CI	
Antibody	Group	Timing	N	(EU/mL)	LL	UL
Anti-PT	Pooled KINRIX	PRE	823	4.0	3.8	4.2
		PI(M1)	849	70.7	66.8	74.8
	INFANRIX + IPOL	PRE	257	4.2	3.8	4.7
		PI(M1)	261	80.4	72.4	89.1
Anti-FHA	Pooled KINRIX	PRE	847	50.4	46.2	55.0
		PI(M1)	850	864.2	821.0	909.8
	INFANRIX + IPOL	PRE	262	53.2	45.2	62.5
		PI(M1)	261	939.7	858.3	1028.8
Anti-PRN	Pooled KINRIX	PRE	847	27.0	24.9	29.2
		PI(M1)	851	598.7	559.2	640.9
	INFANRIX + IPOL	PRE	262	27.4	23.5	32.0
		PI(M1)	261	593.8	525.7	670.7

GMC = geometric mean antibody concentration
N = number of subjects with available results
95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit
PRE =pre-vaccination blood sample at Day 0
PI(M1) =post-vaccination blood sample at Month 1
Source: 125260/0.1, m5.3.5.1.3, 048-report-body.pdf, page 96

Table 23 presents seropositivity rates and GMTs for anti-poliovirus type 1, type 2, and type 3 antibodies at baseline and one month after vaccination.

Table 23. Study 213503/048 Percentage of subject with seropositivity rates and GMTs for anti-poliovirus type 1, anti-poliovirus type 2, anti-poliovirus type 3 antibodies before and one month after vaccination (ATP Cohort for Immunogenicity)

				≥**1:8**				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-poliovirus type 1	Pooled KINRIX	PRE	837	739	88.3	85.9	90.4	31.5	29.0	34.1
		PI(M1)	825	824	99.9	99.3	100	2109.1	1967.0	2261.4
	INFANRIX + IPOL	PRE	261	222	85.1	80.1	89.2	30.7	26.2	36.0
		PI(M1)	249	249	100	98.5	100	1683.1	1444.7	1960.9
Anti-poliovirus type 2	Pooled KINRIX	PRE	842	773	91.8	89.7	93.6	39.7	36.6	43.1
		PI(M1)	818	818	100	99.6	100	2266.2	2121.0	2421.3
	INFANRIX + IPOL	PRE	262	228	87.0	82.3	90.8	35.3	30.1	41.3
		PI(M1)	252	252	100	98.5	100	1802.0	1566.3	2073.2
Anti-poliovirus type 3	Pooled KINRIX	PRE	841	712	84.7	82.0	87.0	37.6	34.0	41.5
		PI(M1)	798	798	100	99.5	100	3563.0	3327.7	3814.9
	INFANRIX + IPOL	PRE	260	221	85.0	80.1	89.1	38.2	31.7	45.9
		PI(M1)	239	239	100	98.5	100	3367.8	2923.3	3879.8

N = number of subjects with available results
n/% = number/percentage of subjects with titer within the specified range
GMT = geometric mean antibody titer
95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit
PRE = pre-vaccination blood sample at Day 0
PI(M1) = post-vaccination blood sample at Month 1
Source: 125260/0.1, m5.3.5.1.3, 048-report-body.pdf, page 99

Table 24 presents the proportions of subjects with booster responses to poliovirus type 1, type 2, and type 3 antibodies, according to seropositivity status.

Table 24. Study 213503/048 Percentage of subjects with booster responses for anti-poliovirus type 1, anti-poliovirus type 2 and anti-poliovirus type 3 antibodies one month after vaccination (ATP Cohort for Immunogenicity)

				Booster Response			
						95% CI	
Antibody	Group	Pre-vaccination status	N	n	%	LL	UL
Anti-poliovirus type 1	Pooled KINRIX	S-	97	97	100	-	-
		S+	712	688	96.6	-	-
		Total	809	785	97.0	95.6	98.1
	INFANRIX + IPOL	S-	38	38	100	-	-
		S+	211	193	91.5	-	-
		Total	249	231	92.8	88.8	95.7
Anti-poliovirus type 2	Pooled KINRIX	S-	63	63	100	-	-
		S+	744	718	96.5	-	-
		Total	807	781	96.8	95.3	97.9
	INFANRIX + IPOL	S-	33	32	97.0	-	-
		S+	219	202	92.2	-	-
		Total	252	234	92.9	88.9	95.7
Anti-poliovirus type 3	Pooled KINRIX	S-	118	118	100	-	-
		S+	669	642	96.0	-	-
		Total	787	760	96.6	95.0	97.7
	INFANRIX + IPOL	S-	32	32	100	-	-
		S+	205	188	91.7	-	-
		Total	237	220	92.8	88.8	95.8

S+ = subjects with titers ≥1:8
S- = subjects with titers <1:8
Total = subjects either seropositive or seronegative at pre-vaccination
N = number of subjects with available results at PRE and POST time point
n/% = number/percentage of subjects with a booster response
95% CI = exact 95% confidence interval; LL = Lower Limit; UL = Upper Limit
Booster response defined as:
For initially seronegative subjects, antibody titer ≥1:32 at PI(M1)
For initially seropositive subjects, antibody titer at PI(M1) ≥4 fold the pre-vaccination antibody titer
Source: 125260/0.1, m5.3.5.1.3, 048-report-body.pdf, page 100

6.1.2.3 Safety Outcomes

The percentages of subjects reporting any local symptom, any general symptom, and any unsolicited adverse event were similar between the three KINRIX lots (data presented in BLA). There were no apparent clinically relevant differences in the reporting of specific adverse events between the three KINRIX lots (data presented in BLA). Thus, in this review, safety analyses will be presented for the pooled KINRIX group and the INFANRIX + IPOL Group.

6.1.2.3.1 Solicited Adverse Events

Solicited local adverse events occurred more commonly at the KINRIX or INFANRIX injection sites than at the IPOL or MMR_{II} injection sites. Table 25 presents the percentage of subjects who reported solicited local adverse events at the KINRIX or INFANRIX injection site, according to intensity, during the 4-day follow-up period after vaccination. The frequencies of any pain and grade 3 pain were statistically significantly higher at the KINRIX injection site than at the INFANRIX injection site (Table 25). When any injection site was considered (i.e., KINRIX,

INFANRIX, IPOL or MMR_{II}), the frequency of grade 3 pain during the 4-day period post-vaccination period also was statistically significantly higher in the KINRIX group than the Control group; the frequency of injection site redness ≥100 mm was statistically significantly higher in the Control group than the KINRIX group (data in BLA; not shown in this review).

Table 25. Study 213503/048 Percentage of subjects reporting the occurrence of solicited local symptoms at the KINRIX or INFANRIX injection site during the 4-day follow-up period after vaccination (Total Vaccinated Cohort)*

Symptom	Intensity	Pooled KINRIX					INFANRIX + IPOL					p-value
		N	n	%	95% CI		N	n	%	95% CI		
					LL	UL				LL	UL	
Pain	Any	3128	1783	57.0	55.2	58.7	1043	556	53.3	50.2	56.4	0.040
	Grade ≥2	3128	430	13.7	12.6	15.0	1043	125	12.0	10.1	14.1	0.155
	Grade 3	3128	49	1.6	1.2	2.1	1043	6	0.6	0.2	1.2	0.012
	Medical advice	3128	26	0.8	0.5	1.2	1043	13	1.2	0.7	2.1	0.264
Redness (mm)	Any	3126	1144	36.6	34.9	38.3	1039	380	36.6	33.6	39.6	1.000
	> 20	3126	837	26.8	25.2	28.4	1039	294	28.3	25.6	31.1	0.354
	≥ 50	3126	551	17.6	16.3	19.0	1039	208	20.0	17.6	22.6	0.086
	≥ 80	3126	233	7.5	6.6	8.4	1039	94	9.0	7.4	11.0	0.110
	≥ 110	3126	90	2.9	2.3	3.5	1039	43	4.1	3.0	5.5	0.053
	Medical advice	3126	63	2.0	1.6	2.6	1039	25	2.4	1.6	3.5	0.456
Swelling (mm)	Any	3121	811	26.0	24.5	27.6	1040	281	27.0	24.3	29.8	0.515
	> 20	3121	570	18.3	16.9	19.7	1040	188	18.1	15.8	20.6	0.926
	≥ 50	3121	318	10.2	9.1	11.3	1040	120	11.5	9.7	13.6	0.221
	≥ 80	3121	113	3.6	3.0	4.3	1040	45	4.3	3.2	5.7	0.303
	≥ 110	3121	44	1.4	1.0	1.9	1040	19	1.8	1.1	2.8	0.378
	Medical advice	3121	59	1.9	1.4	2.4	1040	24	2.3	1.5	3.4	0.442
Increase in mid-upper arm circumference (mm)	Any	3121	1124	36.0	34.3	37.7	1041	394	37.8	34.9	40.9	0.298
	> 10	3121	486	15.6	14.3	16.9	1041	181	17.4	15.1	19.8	0.172
	> 20	3121	215	6.9	6.0	7.8	1041	77	7.4	5.9	9.2	0.576
	> 30	3121	74	2.4	1.9	3.0	1041	33	3.2	2.2	4.4	0.174
	Medical advice	3121	43	1.4	1.0	1.9	1041	19	1.8	1.1	2.8	0.303

*Subjects with no daily measurement for a particular symptom are eliminated from the cohort.
N = number of subjects with local symptom sheet completed; n/% = number/percentage of subjects reporting the specified symptom during the 4-day follow-up period after vaccination
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit
Any = any symptom with grade or measurement > 0
Grade 2 pain = painful when limb is moved
Grade 3 pain = pain that prevented normal activities
Medical advice = medical advice sought (a visit to or from medical personnel)
p-values <0.05 are indicated in bold.
Source: 125260/0.7, m5.3.5.1.3, 048-additional-data.pdf, pages 19-21; 125260/0.14, m1.11.3, efficacy-12dec2007.pdf, pages 1-2

Table 26 presents the percentage of subjects who reported solicited systemic adverse events, according to intensity, during the 4-day period after vaccination. The frequency of fever >38.0° C was statistically significantly higher in the KINRIX group (6.5%) than the Control group (4.4%) (Table 26). The frequencies of other categories of fever and of drowsiness and loss of appetite were not statistically significantly different between groups (Table 26).

Table 26. Study 213503/048 Percentage of subjects reporting the occurrence of solicited systemic symptoms within 4 days after vaccination (Total Vaccinated Cohort)*

		Pooled KINRIX					INFANRIX + IPOL					p-value
					95 % CI					95 % CI		
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	
Fever (orally) (°C)	≥ 37.5*	3037	487	16.0	14.7	17.4	993	147	14.8	12.7	17.2	0.367
	> 38.0	3037	197	6.5	5.6	7.4	993	44	4.4	3.2	5.9	0.017
	> 38.5	3037	86	2.8	2.3	3.5	993	23	2.3	1.5	3.5	0.431
	> 39.0	3037	33	1.1	0.7	1.5	993	11	1.1	0.6	2.0	1.000
	> 39.5	3037	12	0.4	0.2	0.7	993	5	0.5	0.2	1.2	0.584
	> 40.0	3037	3	0.1	0.0	0.3	993	0	0.0	0.0	0.4	1.000
	Medical advice	3037	37	1.2	0.9	1.7	993	10	1.0	0.5	1.8	0.734
Drowsiness	Grade ≥ 1*	3120	595	19.1	17.7	20.5	1036	181	17.5	15.2	19.9	0.270
	Grade ≥ 2	3120	129	4.1	3.5	4.9	1036	47	4.5	3.4	6.0	0.593
	Grade 3	3120	26	0.8	0.5	1.2	1036	8	0.8	0.3	1.5	1.000
	Medical advice	3120	7	0.2	0.1	0.5	1036	1	0.1	0.0	0.5	0.688
Loss of appetite	Grade ≥ 1*	3120	484	15.5	14.3	16.8	1036	166	16.0	13.8	18.4	0.693
	Grade ≥ 2	3120	91	2.9	2.4	3.6	1036	32	3.1	2.1	4.3	0.752
	Grade 3	3120	24	0.8	0.5	1.1	1036	6	0.6	0.2	1.3	0.673
	Medical advice	3120	9	0.3	0.1	0.5	1036	2	0.2	0.0	0.7	1.000

*Subjects with no daily measurement for a particular symptom are eliminated from the cohort. Subjects with partial daily recording are counted if, over the solicited period, they have at least one daily recording ≥37.5 for fever, or ≥Grade 1 for drowsiness and loss of appetite.
N = number of subjects with general symptom sheet completed; n/% = number/percentage of subjects reporting at least once the symptom
95% CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit
Drowsiness: Grade 1 = Easily tolerated; Grade 2 = Interferes with normal activity; Grade 3 = Prevents normal activity
Loss of appetite: Grade 1 = Eating less than usual/no effect on normal activity; Grade 2 = Eating less than usual/interferes with normal activity; Grade 3 = Not eating at all
Medical advice = medical advice sought (a visit to or from medical personnel)
p-values <0.05 are indicated in bold.
Source: 125260/0.7, m5.3.5.1.3, 048-additional-data.pdf, pages 8 and 15; 125260/0.13, m1.11.3, efficacy-05dec2007.pdf, pages 10-11

6.1.2.3.2 Non-Inferiority Evaluation of Increased Circumferential Limb Swelling

Table 27 shows the primary non-inferiority analysis of increased circumferential swelling at the DTaP-based injection site within 4 days after vaccination. Increased circumferential swelling was defined in the protocol as injection site swelling involving >50% of the upper arm length and with an increase of >30 mm in mid-upper arm circumference.

Table 27. Study 213503/048 Treatment difference in the incidence of increased circumferential swelling at the DTaP-based injection site within 4 days after vaccination (Total Vaccinated Cohort)

							Difference in percentage (Pooled KINRIX minus INFANRIX + IPOL)			Non-inferiority criteria met (Yes/No)
	Pooled KINRIX			INFANRIX + IPOL				95% CI		
	N	n	%	N	n	%	%	LL	UL	
>30 mm increase in mid upper arm circumference compared to baseline and swelling >50% of upper arm length	3156	20	0.6	1053	11	1.0	-0.41	-1.26	0.16	Yes

N = number of subjects having received at least one dose
n (%) = number (percentage) of subjects in the specified category
95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit
Criteria for claiming non-inferiority – upper limit of the 95% CI for the difference between groups in percentage of subjects reporting increased circumferential swelling 2% or less
Source: 125260/0.1, m5.3.5.1.3, 048-report-body.pdf, page 112

6.1.2.3.3 Protocol-Defined "Large Injection Site Swelling"

According to the protocol, "large injection site swelling" was defined as local swelling with a diameter >50 mm, any increased mid-upper arm circumference of any injected limb >30 mm above baseline, or any diffuse swelling that interfered with or prevented everyday activities. If subjects experienced "large injection site swelling" during the 4-day period post-vaccination, the parents were to contact study personnel and arrange to bring their child to the study site for evaluation. At the evaluation, the investigator was to record information further describing the swelling on a standardized swelling report form. For subjects who did not come to the site for evaluation, study personnel solicited the information for the swelling report form by telephone.

Information on the occurrence of protocol-defined "large injection site swelling" at the DTaP-based injection site is presented in Table 28. The data in Table 28 reflect calls from parents to notify the sites of "large injection site swelling", as well as information obtained at the routine phone calls conducted 4-6 days post-vaccination. For two of the three criteria for "large injection site swelling"—i.e. local swelling >50 mm in diameter and increased arm circumference >30 mm above baseline, information was specifically solicited and recorded daily on memory aids. For the third criterion, diffuse swelling preventing or interfering with daily activities, the memory aids did not specifically solicit daily recordings of occurrence.

Table 28. Study 213503/048 Incidence of protocol defined "large injection site swelling" associated with the DTaP injection site reported during the 4-day period after vaccination (Total Vaccinated Cohort)

	Pooled KINRIX N = 3156		INFANRIX + IPOL N = 1053	
Parameters or Categories	Value or n	%	Value or n	%
Local swelling >50 mm*	229	7.3	86	8.2
Increase mid-upper arm circumference >30 mm**	76	2.4	34	3.2
Diffuse swelling preventing or interfering with daily activities	17	0.5	8	0.8
At least one of the protocol defined characteristics	265	8.4	100	9.5

N = number of subjects having received at least one dose
n/percent = number/percentage of subjects reporting a large injection site swelling with the indicated characteristic
* maximum injection site swelling between maximum from daily subject reporting and the swelling report
** maximum circumference increase between maximum from daily subject reporting and the swelling report
Source: 125260/0.1, m5.3.5.1.3, 048-report-body.pdf, page 108

For subjects with protocol-defined "large injection site swelling", data from the swelling report forms completed by the investigators are presented in Table 29. Sources of data for the swelling report form included both follow-up exams to evaluate swelling and follow-up phone calls.

Table 29. Study 213503/048 Characterization of "large injection site swelling" at the DTaP-based injection site reported during the 4-day period after vaccination – subjects with protocol defined "large injection site swelling" (Total Vaccinated Cohort)

		Pooled KINRIX N = 265		INFANRIX + IPOL N = 100	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%
Onset (day)	0	27	10.2	9	9.0
	1	174	65.7	71	71.0
	2	54	20.4	19	19.0
	≥ 3	10	3.8	1	1.0
Duration (day)	0	0	0.0	0	0.0
	1	30	11.3	12	12.0
	2	111	41.9	35	35.0
	3	60	22.6	26	26.0
	4	21	7.9	13	13.0
	≥ 5	42	15.8	14	14.0
	Missing	1	0.4	0	0.0
Time between date of physical examination and extensive swelling onset	1 day	48	18.1	21	21.0
	2 days	42	15.8	15	15.0
	3 days	9	3.4	5	5.0
	4 days	5	1.9	0	0.0
	≥ 5 days	3	1.1	3	3.0
	Missing	158	59.6	56	56.0
Outcome	Recovered	264	99.6	97	97.0
	Recovering	1	0.4	1	1.0
	Ongoing	0	0.0	1	1.0
	Sequelae	0	0.0	1	1.0
Pain	None	69	26.0	26	26.0
	Any	196	74.0	74	74.0
	Grade 1	126	47.5	47	47.0
	Grade 2	61	23.0	24	24.0
	Grade 3	9	3.4	3	3.0
Redness	None	87	32.8	37	37.0
	Any	175	66.0	61	61.0
	1 mm -≤ 20 mm	3	1.1	0	0.0
	21 mm -≤ 50 mm	15	5.7	3	3.0
	51 mm -≤ 100 mm	127	47.9	36	36.0
	> 100 mm	29	10.9	22	22.0
	Exact recording missing	1	0.4	0	0.0
	Missing	3	1.1	2	2.0
Impairment	None	238	89.8	88	88.0
	Any	27	10.2	12	12.0
	Grade 1	5	1.9	3	3.0
	Grade 2	15	5.7	8	8.0
	Grade 3	7	2.6	1	1.0
Induration	None	108	40.8	44	44.0
	Any	157	59.2	56	56.0
	1 mm -≤ 20 mm	2	0.8	1	1.0
	21 mm -≤ 50 mm	7	2.6	5	5.0
	51 mm -≤ 100 mm	118	44.5	42	42.0

	> 100 mm	28	10.6	8	8.0
	Exact recording missing	2	0.8	0	0.0
Fever	None	224	84.5	85	85.0
	Any	37	14.0	12	12.0
	≥ 37.5 °C -≤ 38.0 °C	25	9.4	9	9.0
	> 38.0 °C -≤ 38.5 °C	9	3.4	3	3.0
	> 38.5 °C -≤ 39.0 °C	2	0.8	0	0.0
	> 39.0 °C -≤ 39.5 °C	0	0.0	0	0.0
	> 39.5 °C -≤ 40.0 °C	1	0.4	0	0.0
	> 40.0 °C	0	0.0	0	0.0
	Missing	4	1.5	3	3.0

N = total number of large injection site swelling
n/% = number/percentage of large swellings in a given category excluding subjects with missing recording on the occurrence of the symptom
-All information comes from the extensive swelling report -
Intensity of pain was graded as follows:
Grade 1 = painful on touch
Grade 2 = painful when limb is moved
Grade 3 = pain that prevented normal activities
Functional impairment was graded as follows:
Grade 1 = easily tolerated, causing minimal discomfort and did not interfere with everyday activities
Grade 2 = sufficiently discomforting to interfere with normal everyday activities
Grade 3 = prevented normal everyday activities
Source: 125260/0.1, m5.3.5.1.3, 048-report-body.pdf, pages 108-110

Most “large injection site swelling” reactions were reported to occur within one day following vaccination and resolved within 3 days following vaccination. There were 42 subjects in the Pooled KINRIX Group and 14 subjects in the INFANRIX + IPOL Group who experienced “large injection site swelling” reactions lasting 5 days or longer. For these subjects, the average duration of their swelling reactions was 6.5 days and 5.6 days, respectively. The maximum duration recorded for a large injection site swelling reaction was 33 days, for a subject who had received KINRIX. The majority of the subjects with symptoms lasting longer than 5 days did not require a follow-up visit with the study physician. Six of the 42 subjects in the Pooled KINRIX Group and 1 of the 14 in the INFANRIX + IPOL Group were brought to the clinic for further examination upon the investigator’s request. All of the cases of extensive swelling lasting 5 or more days resolved without sequelae.

One subject in the Pooled KINRIX Group and one subject in the INFANRIX + IPOL group had “large injection site swelling” with outcome listed as recovering. For these two subjects, the last day that the swelling met the protocol-defined criteria for “large injection site swelling” was on Day 2 and Day 3, respectively, after vaccination. For these subjects, the outcome was listed as recovering because complete resolution occurred after the last contact with the investigator to evaluate the swelling.

One subject in the INFANRIX + IPOL Group had “large injection site swelling” with outcome listed as ongoing. The last day that the subject’s swelling met protocol-defined large swelling criteria was on Day 4 following vaccination, and there was no measurable redness or swelling as of Day 7 following vaccination. The listing of the outcome as “ongoing” is presumably due to measurable swelling being present at the time of the 4-6 day telephone contact.

Among subjects with large injection site swelling reactions reported, no subjects in the KINRIX group had sequelae. One subject in the INFANRIX + IPOL Group had sequelae (post-inflammatory hyperpigmentosis) associated with extensive swelling, lasting three days.

6.1.2.3.4 Symptoms that May be Associated with MMR Vaccine

Table 30 presents data on the incidence of fever and other solicited symptoms that may be associated with MMR vaccine during the 15-day post-vaccination period.

Table 30. Study 213503/048 Percentage of subjects with solicited general symptoms that may be associated with MMR vaccine during the 15-day post-vaccination period (Total Vaccinated Cohort)*

		Pooled KINRIX					INFANRIX + IPOL				
					95% CI					95% CI	
Symptom		N	n	%	LL	UL	N	n	%	LL	UL
Rash site	Any	3121	99	3.2	2.6	3.8	1036	36	3.5	2.4	4.8
	Administration site	3121	30	1.0	0.6	1.4	1036	14	1.4	0.7	2.3
	Non administration site	3121	71	2.3	1.8	2.9	1036	23	2.2	1.4	3.3
Non administration site rash	Measles/Rubella-like	3121	13	0.4	0.2	0.7	1036	6	0.6	0.2	1.3
Parotitis	Any	3121	6	0.2	0.1	0.4	1036	3	0.3	0.1	0.8
Suspected signs of meningism	Any	3121	16	0.5	0.3	0.8	1036	5	0.5	0.2	1.1
Fever/(Orally) (°C)	≥ 37.5	3045	646	21.2	19.8	22.7	1000	208	20.8	18.3	23.4
	> 38.0	3045	313	10.3	9.2	11.4	1000	83	8.3	6.7	10.2
	> 38.5	3045	168	5.5	4.7	6.4	1000	47	4.7	3.5	6.2
	> 39.0	3045	83	2.7	2.2	3.4	1000	23	2.3	1.5	3.4
	> 39.5	3045	31	1.0	0.7	1.4	1000	8	0.8	0.3	1.6
	> 40.0	3045	8	0.3	0.1	0.5	1000	1	0.1	0.0	0.6
	Medical advice	3045	63	2.1	1.6	2.6	1000	19	1.9	1.1	3.0

* For fever, subjects with no daily measurement are eliminated from the cohort. Subjects with partial daily temperature recording are counted if, over the solicited period, they have at least one daily recording ≥37.5°C.
15- day follow-up period = Day 0 - Day 14
N = number of subjects with general symptom sheet completed
n/% = number/percentage of subjects reporting a specified symptom
95% CI = exact 95% confidence interval; LL = lower limit; UL = upper limit
Medical advice = medical advice sought (a visit to or from medical personnel)
Source: 125260/0.1, 048-report-body.pdf, page 115; 125260/0.7, 048-additional-data.pdf, page 8.

Among KINRIX subjects, "suspected signs of meningism" included headache (8 subjects), emesis (6 subjects), and headache and emesis (2 subjects). Among INFANRIX + IPOL subjects, "suspected signs of meningism" included headache (3 subjects), emesis (1 subject), and febrile seizures (1 subject).

6.1.2.3.5 Unsolicited Adverse Events

Unsolicited adverse events of any intensity within 31 days post-vaccination were reported by 30.5% of subjects in the Pooled KINRIX Group and 29.2% of subjects in the INFANRIX + IPOL Group. In both groups, the most frequently reported unsolicited adverse events were upper respiratory infections (5.7-5.8% of subjects) and cough (3.2-3.4% of subjects).

6.1.2.3.6 Serious Adverse Events

There were no deaths among study subjects during the study period. Table 31 presents serious adverse events reported during the entire study, through 6 months post-vaccination.

Table 31 Study 213503/048 Subjects with serious adverse events reported during the entire study (Total Vaccinated Cohort)

Subject Number	Age (Years)/ Gender	Vaccine Group	Preferred Term (MedDRA)	Time to Onset (Days)	Duration (Days)	Outcome
Active Phase (0-30 days post-vaccination)						
100668	4/Male	Pooled KINRIX	Hypernatraemia Dehydration	2 2	8 8	Resolved Resolved
101658	4/Female	Pooled KINRIX	Cerebrovascular accident	30	-	Not resolved
101841	4/Male	Pooled KINRIX	Gastroenteritis Dehydration	19 19	4 4	Resolved Resolved
101148	4/Female	INFANRIX + IPOL	Constipation	14	25	Resolved
Extended Safety Follow-up Phase (Day 31 to 6 months [minimum 182 days] post-vaccination)						
100577	4/Male	Pooled KINRIX	Gastritis Dehydration	162 162	3 3	Resolved Resolved
100941	4/Male	Pooled KINRIX	Pneumonia necrotizing	172	37	Resolved
101854	4/Female	Pooled KINRIX	Viral infection	43	5	Resolved
102361	4/Male	Pooled KINRIX	Pneumonia	63	11	Resolved
101406	4/Male	Pooled KINRIX	Optic atrophy	180	-	Not Resolved
101825	5/Female	Pooled KINRIX	Subcutaneous abscess Cellulitis	177 177	16 16	Resolved Resolved
103440	4/Male	Pooled KINRIX	Burkitt's lymphoma	155	-	Not resolved
105628	4/Male	Pooled KINRIX	Dehydration	36	2	Resolved
106740	4/Female	Pooled KINRIX	Asthma	140	9	Resolved
100627	4/Male	INFANRIX + IPOL	Pneumonia	39	34	Resolved
101723	4/Female	INFANRIX + IPOL	Viral infection Dehydration	118 118	3 3	Resolved Resolved
105978	5/Male	INFANRIX + IPOL	Appendicitis perforated	108	7	Resolved

Age = age at onset date of serious adverse event
Source: 125260/0.1, 048-report-body.pdf, page 118

Clinical case narratives are provided below for the four serious adverse events that occurred within 30 days following vaccination and for selected serious adverse events that occurred during the extended safety follow-up phase.

Subject 100668 Hypernatremia and dehydration

Two days following vaccination with KINRIX and MMR_{II}, this 4-year old male developed influenza like illness with fever, decreased oral intake, and decreased activity. He was hospitalized and found to have hypernatremia, dehydration, and otitis media. He was treated with intravenous antibiotics and fluids. The hypernatremia and dehydration resolved after 8 days and the subject was discharged from the hospital.

Subject 101658 Cerebrovascular accident

This 4-year old female experienced an ischemic stroke of undetermined etiology 30 days following KINRIX and MMR_{II}. She presented with right-sided weakness, stumbling gait, and abnormal speech. Diffuse stroke in the lenticular striate capsule was confirmed by magnetic

resonance imaging. She was admitted to the pediatric intensive care unit, and was transferred to a rehabilitation facility 6 days later.

Relevant family history included three maternal first cousins with strokes between ages 30 and 40 years, and two maternal first cousins with myocardial infarctions. In addition, the subject's mother had previously experienced a spontaneous abortion, and was noted to have low protein C and was maintained on Lovenox throughout the second and third trimesters while pregnant with the subject. The mother's protein C normalized at some time after the subject's delivery. All results of a "thrombotic risk panel" performed on the subject were described as negative.

Upon discharge from the rehabilitation facility 15 days later the subject was noted to have improvement in neurological and functional parameters. At a study contact with the subject 48 days after the onset of the event, continued improvement was noted but some mild deficits remained. Daily aspirin, as well as regular physical therapy and neurological evaluation, were to be continued. No changes in the subject's condition were reported at the time of the extended safety follow-up contact.

Subject 101841 Gastroenteritis and dehydration
This 4-year old male reported serious adverse events of gastroenteritis and dehydration 19 days following vaccination with KINRIX and MMR_{II}. He was hospitalized with vomiting, diarrhea, fever, and lethargy. Blood and stool cultures were negative. The events, thought to be due to a viral illness, resolved after four days and the subject was discharged.

Subject 101148 Constipation
This four-year old female presented to an emergency room with abdominal pain which started 14 days following vaccination with INFANRIX, IPOL, and MMR_{II}. An abdominal CT scan ruled out a surgical abdomen. The event, diagnosed as constipation, resolved after 25 days.

Subject 101406 Optic atrophy
This 4-year old male reported a serious adverse event of optic atrophy which was diagnosed 180 days following vaccination with KINRIX and MMR_{II}. Approximately 14 months before vaccination, he had been diagnosed with a visual acuity problem. Two months later, an optometry exam revealed myopia not needing treatment. Five days following vaccination, an optometry exam noted "healthy eyes". Approximately 5 months post-vaccination, he was found to have decreased vision. An MRI was scheduled and the results were unknown at the time of the extended safety follow-up contact.

Subject 103440 Burkitt's lymphoma
This 4-year old male was diagnosed with Burkitt's lymphoma 156 days following vaccination with KINRIX and MMR_{II}. He developed jaw pain 108 days after vaccination, and was subsequently hospitalized for evaluation, diagnosed with Burkitt's lymphoma, and started on chemotherapy. The event was ongoing at the time of the extended safety follow-up contact.

6.1.3 Comments and Conclusions
The safety and immunogenicity data from this study support the approval of a single dose of KINRIX in children 4-6 years of age who have previously received four doses of DTaP using INFANRIX and/or PEDIARIX for the first three doses and INFANRIX for the fourth dose, and three doses of IPV. While all children in Study 213503/048 previously received four doses of INFANRIX, the data from this study support use of KINRIX as the fifth DTaP dose following an approved regimen of PEDIARIX and/or INFANRIX since these three vaccines have identical acellular pertussis components. Because of the differences in the types and amounts of pertussis

antigens contained in acellular pertussis vaccines from different manufacturers, the data from this study do not support the use of KINRIX following previous doses of other manufacturers' DTaP vaccine.

6.1.3.1 Study Design and Implementation

The protocol-defined endpoints were clear and appropriate. Review of the data did not identify any concerns with trial implementation. The quality of the data appeared to be acceptable. Subjects were all previously primed with four doses of INFANRIX and three doses of IPOL. KINRIX or U.S. licensed Control vaccines (INFANRIX + IPOL) were administered concomitantly with U.S. licensed MMR_{II}. Subjects did not receive varicella vaccine concomitantly with study vaccines as the study was initiated, and the active phase nearly completed, prior to the June 2006 Advisory Committee on Immunization Practices (ACIP) recommendation for routine administration of a second dose of varicella vaccine at age 4-6 years. See Section 11.2 for the applicant's plan to evaluate KINRIX administered concomitantly with varicella vaccine.

6.1.3.2 Immunogenicity

Although there are well accepted serological correlates of protection for diphtheria, tetanus, and the polioviruses contained in KINRIX, a high proportion of children 4-6 years of age who previously received four doses of DTaP vaccine and three doses of IPV are expected to have seroprotective levels of antibodies to these antigens prior to receipt of their subsequent dose of DTaP vaccine and IPV. Thus, for these antigens, the primary evaluation of the immunogenicity of KINRIX administered as a booster dose in children 4-6 years of age was based on a comparison of diphtheria and tetanus booster responses and GMTs of antibodies to the three polioviruses, relative to children who received separately administered INFANRIX and IPOL. For pertussis, for which there is not a well accepted serological correlate of protection, the primary evaluation of the immunogenicity of KINRIX administered as a booster dose in children 4-6 years of age was based on a comparison of booster responses to each of the pertussis antigens, relative to children who received INFANRIX. The efficacy of the pertussis component of KINRIX was previously demonstrated in clinical efficacy studies of INFANRIX administered as a three dose series in infants.

All pre-specified primary immunogenicity endpoints for lot consistency of KINRIX were met, justifying use of the pooled KINRIX groups for the non-inferiority immunogenicity evaluations. Based on the results of pre-specified primary analyses, KINRIX was shown to be non-inferior to separately administered INFANRIX + IPOL with regard to booster responses to diphtheria, tetanus and the pertussis antigens and GMTs to the polioviruses.

6.1.3.3 Safety

Local injection site reactions occurred commonly at the KINRIX and INFANRIX injection sites. Within four days following vaccination with KINRIX, injection site pain, redness, swelling, and increase in mid-upper arm circumference were reported in 57%, 37%, 26%, and 36% of subjects, respectively. Following INFANRIX, the frequencies of these local reactions were 53%, 37%, 27%, and 38%, respectively. Within four days post-vaccination, injection site pain that prevented normal activities was reported in 1.6% of subjects following KINRIX and 0.6% of subjects following INFANRIX. Within four days post-vaccination, protocol-defined "large injection site swelling" (local swelling >50 mm, increase in mid-upper arm circumference >30 mm, or any diffuse swelling that prevented or interfered with daily activities) was reported in 8.4% of subjects following KINRIX and 9.5% of subjects following INFANRIX. During the four day post-vaccination period, among solicited local reactions, injection site pain of any intensity and

injection site pain that prevented normal activities were statistically significantly more frequent following KINRIX than INFANRIX.

Based on the results of a pre-specified primary analysis, KINRIX was shown to be non-inferior to INFANRIX with regard to increased circumferential swelling at the injection site within four days following vaccination. Increased circumferential swelling, defined as an injection site swelling diameter that involves >50% of the length of the upper arm that is also associated with a >30 mm increase of the mid-upper arm circumference compared to the baseline measurement, occurred at the KINRIX injection site in 0.6% of subjects and at the INFANRIX injection site in 1.0% of subjects.

For historical perspective, it should be noted that increasing frequency of local injection site reactions with successive doses in the recommended five-dose DTaP series has been described previously for U.S. licensed DTaP vaccines, including INFANRIX. Extensive swelling of the injected limb has been described previously following booster doses of some DTaP vaccines, including INFANRIX.

The rate of fever >38^{o}C during the four day period post-vaccination was statistically significantly higher in the KINRIX group (6.5%) than the INFANRIX + IPOL group (4.4%). There were no statistically significant differences between groups in the occurrence of other categories of fever or in the proportion of subjects seeking medical advice for fever.

There were no notable imbalances in the overall occurrence of serious adverse events among subjects who received KINRIX relative to those who received INFANRIX + IPOL. The subject who experienced an ischemic stroke of undetermined etiology 30 days following receipt of KINRIX was reported to have a family history of thrombotic events. Nonetheless, the occurrence of this event prompted a review of GSK Biologicals' global safety database for cerebrovascular accident and thrombotic events following DTaP-IPV, INFANRIX, and PEDIARIX. The results of this review were presented in Section 5.1.2.2. The incidence of childhood arterial ischemic stroke, as reported by population-based studies and hospital discharge surveys, ranges from 0.6 to 7.9 per 100,000 children ages 0-18 years of age. (1) While many risk factors for stroke in children have been reported, in up to one third of cases no cause is identified. (1)

The study was not designed to evaluate demographic characteristics that might predict a greater risk of adverse events or to evaluate the safety of KINRIX in subjects with underlying illnesses.

6.2 Supportive Trial #1

6.2.1 Applicant's Protocol # and Protocol Title

Study 213503/047: Open, randomized, phase II, clinical trial to compare the immunogenicity and safety of a booster dose of GSK Biologicals' DTaP-IPV vaccine (Infanrix®-IPV) co-administered with a booster dose of Merck and Company's M-M-R®II, to that of separate injections of GSK Biologicals' DTaP vaccine (Infanrix®), Aventis Pasteur's IPV (IPOL®) and M-M-R®II administered as booster doses to healthy children 4 to 6 years of age

6.2.1.1 Objective/Rationale

This study was conducted to assess the safety and immunogenicity of GSK Biologicals' DTaP-IPV vaccine as compared to DTaP and IPV vaccines administered separately.

6.2.1.2 Design Overview
The study was an open, randomized, phase II clinical trial with two parallel groups (DTaP-IPV and INFANRIX + IPOL). Treatment allocation was randomized and balanced 1:1.

6.2.1.3 Population
The study period through the end of the 6-month safety follow-up was 11/21/02 through 9/13/04. Subjects were enrolled from 14 U.S. sites.

Inclusion and Exclusion Criteria
The inclusion and exclusion criteria were essentially the same as those in Study 213053/048 (see Section 6.1.1.3) with the notable exception of poliovirus vaccination priming. Subjects who had received three doses of poliovirus-containing vaccine (either two doses of IPV followed by one dose of OPV, or IPV exclusively) during the first 2 years of life could be enrolled in the study. Poliovirus vaccination priming with two or more doses of OPV was an exclusion criterion. The last two exclusion criteria listed for Study 213503/048 regarding blood dyscrasias and malignant neoplasms affecting the bone marrow or lymphatic systems and family history of congenital or hereditary immunodeficiency (Section 6.1.1.3) were not exclusion criteria in Study 213503/047.

Concomitant Products
All subjects received MMR_{II} concomitantly with DTaP-IPV or Control vaccines (see Section 6.2.1.4).

The use of routine antipyretic/analgesic prophylaxis was discouraged. Parents/guardians were counseled to only use antipyretics/analgesics for treatment of adverse events post-vaccination.

6.2.1.4 Products Mandated by the Protocol

Dosage and administration of study vaccines
At the first study visit, subjects received a single dose of DTaP-IPV or of INFANRIX and IPOL administered separately, co-administered at a separate site, with MMR_{II}. Table 32 presents the dosage, route, and site of administration of the study vaccines.

Table 32. Study 213503/047: Dosage and administration of study vaccines

Group	Visit	Vaccination	Dose	Route	Site	Side
DTaP-IPV	1	DTaP-IPV MMR_{II}	0.5 mL 0.5 mL	IM SC	Deltoid Deltoid	Left Right
INFANRIX+ IPOL	1	INFANRIX IPOL MMR_{II}	0.5 mL 0.5 mL 0.5 mL	IM SC SC	Deltoid Deltoid Deltoid	Left Lower Right Upper Right

IM = intramuscular
SC = subcutaneous

Formulation of study vaccines
The formulation of DTaP-IPV used in this study is as stated in Section 1.2.3, with the exception that it also contained ≤2.5 mg of 2-phenoxyethanol (as preservative) per dose. A single lot of DTaP-IPV, Lot 20787A9, was used.

See Section 6.1.1.4 for the formulation of INFANRIX, IPOL, and MMR_{II}.

6.2.1.5 Endpoints

As indicated in Section 5.3, the pertussis, diphtheria, and tetanus assay validation information provided for this study were not considered adequate by CBER product reviewers. Thus, the endpoints and analyses for pertussis, diphtheria and tetanus immunogenicity will not be presented in this review.

6.2.1.5.1 Primary Immunogenicity Endpoints-- Polioviruses

- Anti-poliovirus type 1, type 2, and type 3 antibody titers one month post-vaccination.

6.2.1.5.2 Secondary Immunogenicity Endpoints—Polioviruses, Measles, Mumps, Rubella

- Anti-poliovirus type 1, type 2, and type 3 booster responses defined as follows:
    - initially seronegative subjects (pre-booster antibody titers below cut-off: <1:8 by neutralization) should have an increase of at least four times the cut-off, one month after vaccination (post-booster antibody titer ≥1:32)
    - initially seropositive subjects (pre-booster antibody titers ≥1:8 by neutralization) should have an increase of at least four times the pre-booster antibody titer, one month after vaccination.
- Anti-poliovirus type 1, type 2, and type 3 seroprotection status (antibody titer ≥1:8 by neutralization)
- Anti-measles, anti-mumps, and anti-rubella antibody concentrations or titers
- Anti-measles antibody concentration ≥150 mIU/mL by ELISA
- Anti-mumps antibody concentration ≥1:28 by neutralization
- Anti-rubella seroprotection status (antibody concentration ≥10 IU/mL by ELISA)
- Anti-rubella seropositivity status (antibody concentration ≥4 IU/mL by ELISA)

6.2.1.5.3 Secondary Safety Endpoints

The secondary safety endpoints evaluated in Study 213503/048 (Section 6.1.1.5.4) were also evaluated in Study 213503/047.

6.2.1.6 Surveillance/Monitoring

6.2.1.6.1 Immunogenicity Monitoring

For all subjects, a 4.0 mL sample of blood was to be collected pre-vaccination (during Visit 1) and post-vaccination (during Visit 2; 30 to 42 days after Visit 1). Table 33 provides summary information on the poliovirus, measles, mumps, and rubella assays.

Table 33. Study 213503/047 Serological assays for polioviruses, measles, mumps, and rubella

Marker	Assay method	Assay cut-off	Assay unit	Laboratory
anti-poliovirus type 1	Neutralization	1:8	dilution titer	----------
anti-poliovirus type 2	Neutralization	1:8	dilution titer	----------
anti-poliovirus type 3	Neutralization	1:8	dilution titer	----------
Measles	ELISA	150	mIU/mL	GSK Biologicals, Rixensart, Belgium
Mumps	Neutralization	1:28	dilution titer	GSK Biologicals, Rixensart, Belgium
Rubella	ELISA	4	IU/mL	GSK Biologicals, Rixensart, Belgium

6.2.1.6.2 Safety Surveillance/Monitoring

In general, the safety monitoring procedures described for Study 213503/048 (Section 6.1.1.6.2) also were followed in Study 213503/047. In Study 213503/047, solicited local and systemic reactions were monitored using diary cards for 15 days (Days 0-14) post-vaccination. Symptoms

that may be associated with MMR vaccination were monitored for 43 days (Days 0-42) post-vaccination.

6.2.1.7 Statistical Considerations

6.2.1.7.1 Randomization
Treatment allocation at the investigator site was performed using a central Internet based randomization system. The randomization algorithm used a minimization procedure accounting for center and poliovirus vaccination history (either sequential IPV-OPV or IPV only), each with equal weight. Upon providing the eligible subject's date of birth and poliovirus vaccination history, the randomization system determined the vaccine number to be used for the subject.

6.2.1.7.2 Sample Size
The target sample size was 400 enrolled subjects to attain 360 subjects evaluable for the primary immunogenicity analyses. The enrollment aim was to include at least 200 subjects who had been primed with three doses of IPV.

With 180 evaluable subjects per group, the statistical power was >99% to rule out a 2-fold decrease in the GMT ratio for each of the three poliovirus antigens one month after vaccination with DTaP-IPV vaccine as compared to INFANRIX + IPOL.

6.2.1.7.3 Study Cohorts/Data Sets Analyzed

Total Vaccinated Cohort
The Total Vaccinated Cohort included all vaccinated subjects. For the total analysis of safety, this included all enrolled and vaccinated subjects for whom post-vaccination safety data were available. The primary analyses of safety were based on the Total Vaccinated Cohort and were performed per treatment actually administered.

ATP Cohort for Safety
The ATP cohort for analysis of safety included all vaccinated subjects for whom administration site of study vaccine/comparator was known and who had not received a vaccine not specified or forbidden in the protocol.

ATP Cohort for Immunogenicity
The ATP Cohort for Immunogenicity included all subjects from the ATP Cohort for Safety who met all eligibility criteria, complied with protocol procedures, and for whom assay results were available for antibodies against at least one study vaccine antigen at least for the post-vaccination samplings. For inclusion in the ATP Cohort for Immunogenicity, the protocol-defined interval between Visits 1 and 2 needed to be at least 30 days and not exceed 42 days. At the time of data analysis, for the ATP Cohort for Immunogenicity, this interval was expanded to be at least 21 days and to not exceed 133 days. The applicant presented results based on the ATP Cohort for Immunogenicity using an interval of 21-133 days, as well as on the protocol-defined ATP Cohort for Immunogenicity using an interval of 30-42 days.

Extended Safety Follow-up (ESFU) Cohort
The ESFU cohort included all vaccinated subjects who had safety follow-up beyond Day 30 as documented by either a 6 month telephone contact or an adverse event reported after Day 30.

6.2.1.7.4 Analyses

Between group analyses of safety and immunogenicity were considered exploratory. For the analyses of post-vaccination poliovirus GMTs, 95% CIs of the GMT ratios (DTaP + IPV divided by DTaP-IPV) were computed using an ANCOVA model that included the vaccine group as fixed effect and the prevaccination titer as regressor. For between group safety analyses, a p-value below 0.05 was used to identify potential differences between groups.

6.2.2 Results

6.2.2.1 Populations Enrolled/Analyzed

The active phase of the study was defined as the period from vaccination through 31 days post-vaccination. The ESFU phase was defined as the period from Day 31 to 6 months (minimum 180 days) post-vaccination. For the analysis of the active phase, a withdrawal was any subject who did not return for the end of the active phase (Visit 2). For the analysis of the ESFU phase, a withdrawal was any subject who did not participate in the concluding study contact. No subject withdrew from the active phase or the ESFU phase as a result of an adverse event. Tables 34 and 35 present the number of subjects enrolled, vaccinated, completed, and withdrawn, by group and reason, in the active phase and the ESFU phase, respectively.

Table 34. Study 213503/047 Number of subjects enrolled, vaccinated, completed, and withdrawn with reason for withdrawal for the active phase (Total Vaccinated Cohort)

	Group		
	DTaP-IPV	INFANRIX + IPOL	Total
Active Phase			
Number of subjects enrolled	200	200	400
Number of subjects vaccinated	200	200	400
Number of subjects completed	193	195	388
Number of subjects withdrawn	7	5	12
Reasons for withdrawal:			
Adverse Event	0	0	0
Protocol violation	0	0	0
Consent withdrawal (not due to an adverse event)	3	1	4
Migrated/moved from study area	0	0	0
Lost to follow-up	4	4	8
Others	0	0	0

Vaccinated = number of subjects who where vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawal = number of subjects who did not come for the last study visit
Source: 125260/0.1, m5.3.5.1.1, 047-report-body.pdf, page 72

Table 35. Study 213503/047 Number of subjects included, completed, and withdrawn with reason for withdrawal for the ESFU phase (Total Vaccinated Cohort)

	Group		Total
	DTaP-IPV	INFANRIX + IPOL	
ESFU Phase			
Number of subjects vaccinated in the active phase	200	200	400
Number of subjects included in the ESFU cohort*	195	196	391
Number of vaccinated subjects with ESFU completed*†	194	195	389
Number of subjects withdrawn from the ESFU phase	6	5	11
Reason for withdrawal:			
Consent withdrawal (not due to an adverse event)	3	1	4
Lost to follow-up ‡	3	4	7

ESFU = Extended Safety Follow-up period of 5 months (from Visit 2 to 6 months [minimum 180 days] post-vaccination)
Completed = number of subjects who completed the concluding contact
Withdrawn = number of subjects who could not be contacted for the concluding contact
*Three subjects (two in the DTaP-IPV group and one in the INFANRIX + IPOL group) were lost to follow-up during the active phase but contributed data for the ESFU phase.
†One subject in the DTaP-IPV group and one subject in the INFANRIX + IPOL group were unable to be contacted at the completion of the ESFU contact, but had earlier contacts during the ESFU Phase. These subjects were included in the ESFU cohort but were not included in the ESFU completed cohort.
‡Two subjects were lost to follow-up in the active phase yet completed the ESFU phase.
Source: 125260/0.1, m5.3.5.1.1, 047-report-body.pdf, page 72

Table 36 presents a summary of the subjects enrolled and included in the analyses performed as well as those excluded and the reason for elimination.

Table 36. Study 213503/047 Number of subjects enrolled and excluded from analyses

	Total n (s)	Percent	DTaP-IPV n (s)	INFANRIX + IPOL n (s)
Active Phase				
Total enrolled cohort	400	-	200	200
Total vaccinated cohort	400	100	200	200
MMR not administered	1(1)		0 (0)	1 (1)
First and second dose of DTaP not INFANRIX	1(1)		1 (1)	0 (0)
ATP safety cohort	398	99.5	199	199
Pre-vaccination blood sample not obtained	5(5)		3 (3)	2 (2)
Post-vaccination blood sample not obtained	22(22)		13 (13)	9 (9)
Serological data incoherent	3(4)		2 (2)	1 (2)
ATP immunogenicity cohort (interval between Visit 1 and Visit 2: 21-133 days)	368	92.0	181	187
ATP immunogenicity cohort (interval between Visit 1 and Visit 2: 30-42 days)	343	85.6	170	173
ESFU Phase				
Total vaccinated cohort	400	100	200	200
Consent withdrawal, lost to follow-up, and did not report an adverse event after Day 30	9		5	4
Extend Safety Follow-up cohort	391	97.8	195	196

Percent = percentage of subjects in the considered ATP cohort relative to the Total Vaccinated Cohort.
Subjects may have more than one elimination code assigned. Each elimination reason n (s) is provided where:
n= number of subjects with the elimination code assigned excluding subjects assigned a lower elimination code number
s= number of subjects with the elimination code assigned
Source: 125260/0.1, m5.3.5.1.1, 047-report-body.pdf, page 73

Table 37 summarizes the demographic characteristics of subjects in the Total Vaccinated Cohort.

Table 37. Study 213503/047 Summary of demographic characteristics (Total Vaccinated Cohort)

		DTaP-IPV N= 200		INFANRIX + IPOL N= 200		Total N= 400	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Age(Years)	Mean	4.1	--	4.1	--	4.1	--
	Standard deviation	0.29		0.23		0.3	
	Median	4.0	-	4.0	-	4.0	-
	Minimum	4	-	4	-	4	-
	Maximum	5	-	5	-	5	-
Gender	Female	107	53.5	99	49.5	206	51.5
	Male	93	46.5	101	50.5	194	48.5
Race	Black	23	11.5	21	10.5	44	11.0
	White/Caucasian	118	59.0	101	50.5	219	54.8
	Oriental	1	0.5	7	3.5	8	2.0
	American Hispanic	32	16.0	35	17.5	67	16.8
	Other	26	13.0	36	18.0	62	15.5

Source: 125260/0.1, m5.3.5.1.1, 047-report-body.pdf, page 75

Table 38 presents the poliovirus vaccination history for the ATP Cohort for Immunogenicity. For the Total Vaccinated Cohort, the proportion of subjects in the DTaP-IPV and INFANRIX + IPOL groups who previously received 3 doses of IPV was 90.5% and 89.5%, respectively.

Table 38. Study 213503/047 Poliovirus vaccination history (ATP Cohort for Immunogenicity)

Vaccination history	DTaP-IPV (N = 181)		INFANRIX + IPOL (N = 187)		Total (N = 368)	
	N	%	N	%	N	%
3 doses of IPV	166	91.7	167	89.3	333	90.5
Sequential IPV-OPV vaccination*	15	8.3	20	10.7	35	9.5

*two doses of IPV vaccine and one dose of OPV vaccine
Source: 125260/0.1, m5.3.5.1.1, 047-report-body.pdf, page 76

6.2.2.2 Immunogenicity Outcomes-- Polioviruses, Measles, Mumps, and Rubella

As indicated in Section 5.3, the immunogenicity data on pertussis, diphtheria, and tetanus will not be presented in this review because CBER product reviewers viewed the validation information submitted for the assays as inadequate.

Among subjects in the ATP Cohort for Immunogenicity who previously received three doses of IPV, prior to vaccination 91.3% to 98.0% (depending on group and poliovirus type) had poliovirus antibody levels $\geq$1:8; following vaccination, 100% had an antibody level $\geq$1:8 for each of the three poliovirus types.

Table 39 presents the two-sided 95% confidence intervals for the adjusted ratios of anti-poliovirus types 1, 2 and 3 GMTs in the INFANRIX + IPOL group and the DTaP-IPV group one month after vaccination for subjects in the protocol-defined ATP immunogenicity cohort (interval between Visit 1 and Visit 2 30-42 days) who previously received three doses of IPV.

Table 39. Study 213503/047 Adjusted GMT ratios of anti-poliovirus type 1, type 2, and type 3 between DTaP-IPV and INFANRIX + IPOL groups one month after vaccination (protocol-defined ATP Cohort for Immunogenicity-- subjects who previously received 3 doses of IPV)

Antibody	DTaP-IPV		INFANRIX + IPOL		Adjusted Ratio (INFANRIX + IPOL /DTaP-IPV)		
	N	Adjusted GMT	N	Adjusted GMT	Adjusted GMT ratio	95% CI	
						LL	UL
Anti-poliovirus type 1	143	1264.7	139	1197.8	0.947	0.766	1.171
Anti-poliovirus type 2	143	1170.6	138	1117.4	0.955	0.775	1.176
Anti-poliovirus type 3	134	2007.1	136	1970.5	0.982	0.761	1.266

Note: Table includes only subjects in the protocol-defined ATP Cohort for Immunogenicity (interval between Visit 1 and Visit 2, 30-42 days) who had received three previous doses of IPV.
N = number of subjects with both pre- and post-vaccination results available
GMT = geometric mean antibody titer, adjusted for baseline titer by ANCOVA
95% CI = two-sided 95% confidence interval; LL = lower limit, UL = upper limit
Source: 125260/0.1, m5.3.5.1.1, 047-report-body.pdf, page 145

Table 40 presents the two-sided 95% confidence intervals for the booster response rates for anti-poliovirus types 1, 2 and 3 in the INFANRIX + IPOL group and the DTaP-IPV group one month after vaccination for subjects in the protocol-defined ATP immunogenicity cohort who previously received three doses of IPV.

Table 40. Study 213503/047 Differences in booster responses to anti-poliovirus type 1, type 2, and type 3 between the DTaP-IPV and INFANRIX + IPOL groups one month after vaccination (protocol-defined ATP Cohort for Immunogenicity-- subjects who previously received 3 doses of IPV)

Antibody	DTaP-IPV			INFANRIX + IPOL			Difference in booster response rate (INFANRIX + IPOL minus DTaP-IPV)		
								95% CI	
	N	n	%	N	n	%	Value (%)	LL	UL
anti-poliovirus type1	143	126	88.1	139	119	85.6	-2.50	-10.63	5.51
anti-poliovirus type 2	143	124	86.7	138	111	80.4	-6.28	-15.12	2.42
anti-poliovirus type 3	134	114	85.1	136	113	83.1	-1.99	-10.85	6.88

Note: Table includes only subjects in the protocol-defined ATP Cohort for Immunogenicity (interval between Visit 1 and Visit 2, 30-42 days) who had received three previous doses of IPV.
N = number of subjects with both pre- and post-vaccination results available
n/% = number/percentage of subjects with a booster response post-vaccination. See Section 6.2.1.5.2 for definition of booster response.
95% CI = Standardized asymptotic 95% confidence interval for the difference; LL = lower limit, UL = upper limit
Source: 125260/0.1, m5.3.5.1.1, 047-report-body.pdf, page 144

Table 41 presents the seropositivity rates and GMCs or GMTs for anti-measles and anti-mumps antibodies and Table 42 presents the seropositivity and seroprotection rates and GMCs for anti-rubella antibodies before and one month after vaccination.

Table 41. Study 213503/047 Percentage of subjects with anti-measles antibody concentrations of at least 150 mIU/mL, with anti-mumps antibody titer of at least 1:28 and anti-measles GMCs and anti-mumps GMTs before and one month after vaccination by pre-vaccination serostatus (ATP Cohort for Immunogenicity*)

Group	Pre-Vaccination status	Timing	N	Seropositive				GMC or GMT		
				n	%	95% CI		mIU/mL	95% CI	
						LL	UL	or titer	LL	UL
Anti-measles										
DTaP-IPV + MMR	S-	Pre	2	0	0.0	0.0	84.2	75.0	75.0	75.0
		PI(M1)	2	2	100	15.8	100	3785.9	577.1	24835.0
	S+	Pre	179	179	100	98.0	100	4432.3	3918.2	5013.8
		PI(M1)	179	179	100	98.0	100	5756.0	5248.1	6313.0
	Total	Pre	181	179	98.9	96.1	99.9	4236.9	3694.1	4859.5
		PI(M1)	181	181	100	98.0	100	5729.4	5227.9	6279.0
INFANRIX + IPOL + MMR	S-	Pre	0	-	-	-	-	-	-	-
	S+/Total	Pre	187	187	100	98.0	100	4684.9	4155.3	5282.0
		PI(M1)	187	187	100	98.0	100	5344.0	4818.2	5927.2
Anti-mumps										
DTaP-IPV + MMR	S-	Pre	2	0	0.0	0.0	84.2	14.0	14.0	14.0
		PI(M1)	2	2	100	15.8	100	120.8	0.0	1.41E10
	S+	Pre	173	173	100	97.9	100	267.5	232.4	308.0
		PI(M1)	168	168	100	97.8	100	450.6	394.0	515.3
	Total	Pre	175	173	98.9	95.9	99.9	258.7	223.3	299.6
		PI(M1)	170	170	100	97.9	100	443.7	387.0	508.6
INFANRIX + IPOL + MMR	S-	Pre	0	-	-	-	-	-	-	-
	S+/Total	Pre	181	181	100	98.0	100	264.2	230.3	303.1
		PI(M1)	171	171	100	97.9	100	404.0	358.4	455.4

*The "expanded" ATP Cohort for Immunogenicity was used. The interval between Visit 1 and Visit 2 could be 21-133 days.
GMC = geometric mean antibody concentration
GMT = geometric mean antibody titer
Seropositivity defined as:
For measles: antibody concentration ≥150 mIU/mL by ELISA
For mumps: antibody titer ≥1:28 by neutralization assay
N = number of subjects with available results
n/% = number/percentage of subjects with antibody concentrations above the specified cut-off
95% CI = 95% exact confidence interval; LL = lower limit; UL = upper limit
S-/ S+ = seronegative/seropositive subjects at pre-vaccination
Pre = pre-vaccination blood sample at Day 0
PI(MI) = post-vaccination blood sample at Month 1
Total = subjects either seronegative or seropositive at pre-vaccination
Source: 125260/0.1, m5.3.5.1.1, 047-report-body.pdf, page 91

Table 42. Study 213503/047 Percentage of subjects with anti-rubella antibody concentrations of at least 4 IU/mL, at least 10 IU/mL and antibody GMCs before and one month after vaccination by pre-vaccination serostatus (ATP Cohort for Immunogenicity*)

Group	Pre-vaccination status	Timing	N	≥4 IU/mL				≥10 IU/mL				GMC		
				n	%	95% CI		n	%	95% CI		IU/mL	95% CI	
						LL	UL			LL	UL		LL	UL
DTaP-IPV + MMR	S-	Pre	1	0	0.0	0.0	97.5	0	0.0	0.0	97.5	2.0	-	-
		PI(M1)	1	1	100	2.5	100	1	100	2.5	100	63.0	-	-
	S+	Pre	180	180	100	98.0	100	179	99.4	96.9	100	71.9	63.2	81.8
		PI(M1)	180	180	100	98.0	100	180	100	98.0	100	152.9	140.0	167.0
	Total	Pre	181	180	99.4	97.0	100	179	98.9	96.1	99.9	70.5	61.7	80.6
		PI(M1)	181	181	100	98.0	100	181	100	98.0	100	152.2	139.3	166.2
INFANRIX + IPOL + MMR	S-	Pre	1	0	0.0	0.0	97.5	0	0.0	0.0	97.5	2.0	-	-
		PI(M1)	1	1	100	2.5	100	1	100	2.5	100	73.0	-	-
	S+	Pre	186	186	100	98.0	100	183	98.4	95.4	99.7	70.5	61.8	80.4
		PI(M1)	186	186	100	98.0	100	186	100	98.0	100	158.1	144.6	173.0
	Total	Pre	187	186	99.5	97.1	100	183	97.9	94.6	99.4	69.2	60.4	79.2
		PI(M1)	187	187	100	98.0	100	187	100	98.0	100	157.5	144.0	172.3

*The "expanded" ATP Cohort for Immunogenicity was used. The interval between Visit 1 and Visit 2 could be 21-133 days.
Seropositivity = antibody concentration ≥4 IU/mL by ELISA
Seroprotection = antibody concentration ≥10 IU/mL by ELISA
GMC = geometric mean antibody concentration
N = number of subjects with available results
S-/ S+ = seronegative/seropositive subjects at pre-vaccination
n/% = number/percentage of subjects with antibody concentrations above the specified cut-off
95% CI = 95% exact confidence interval; LL = lower limit; UL = upper limit
Pre = pre-vaccination blood sample at Day 0
PI(MI) = post-vaccination blood sample at Month 1
Source: 125260/0.1, m5.3.5.1.1, 047-report-body.pdf, page 92

6.2.2.3 Safety Outcomes

6.2.2.3.1 Solicited Adverse Events

In view of the larger sample size of Study 213503/048 and the similarities between studies in monitoring solicited adverse events, the data on these events from Study 213503/047 will not be presented in detail in this review.

In Study 213503/047, the incidence and severity of solicited local and general symptoms were similar between groups. Twenty-six (13%) subjects in the DTaP-IPV group and 29 (14.5%) subjects in the INFANRIX + IPOL group reported protocol-defined "large injection site swelling" at the DTaP-IPV or INFANRIX site within 15 days following vaccination. "Large injection site swelling" was defined as local swelling with a diameter >50 mm and/or any increased mid-upper arm circumference of any injected limb >30 mm above baseline and/or any diffuse swelling that interfered or prevented everyday activities. Of 48 subjects with "large injection site swelling" for whom information on onset date was available, 47 had onset within Days 0-2 post-vaccination; 1 had onset on Day 3 post-vaccination. The characteristics of these reactions in Study 213503/047 were similar to those reported in Study 213503/048.

6.2.2.3.2 Serious Adverse Events

There were no deaths among subjects during the study period. Table 43 presents serious adverse events reported during the entire study, through 6 months post-vaccination.

Table 43. Study 213503/047 Subjects with serious adverse events reported during the entire study (Total Vaccinated Cohort)

Subject Number	Age (Years)/ Gender	Vaccine Group	Preferred Term (MedDRA)	Time to Onset	Outcome
Active Phase					
536	4/Female	INFANRIX + IPOL	Foreign body trauma	9 Days	Resolved
766	4/Male	INFANRIX + IPOL	Cellulitis	20 Days	Resolved
ESFU Phase					
126	5/Female	DTaP-IPV	Asthma Atelectasis	4 Months	Resolved Resolved
280	4/Female	DTaP-IPV	Epilepsy	87 Days	Resolved
380	4/Male	DTaP-IPV	Asthma	46 Days	Resolved

Source: 125260/0.1, m5.3.5.1.1, 047-report-body.pdf, page 111

Clinical case narratives are provided below for the two serious adverse events that occurred within 30 days following vaccination and the case of epilepsy 87 days following vaccination.

Subject 536 Foreign body trauma

Nine days after receiving INFANRIX + IPOL + MMR_{II}, this 4-year old female swallowed a coin. She was hospitalized and received general anesthesia for removal of the object.

Subject 766 Cellulitis

Twenty days after receiving INFANRIX + IPOL + MMR_{II}, this 4-year-old male developed redness to the left eye, followed by swelling a day later. He also had low grade fever. A CT scan showed opacification of bilateral maxillary ethmoid sinuses. The subject was found to have limited left lateral gaze. He was diagnosed with periorbital cellulitis and was hospitalized for intravenous antibiotics. He was discharged after five days, and the event resolved after nine days.

Subject 280 Epilepsy
Eighty-seven days after receiving DTaP-IPV + MMR_{II}, this four-year old female experienced vomiting, movement loss, inability to speak and seizure activity, and was hospitalized. An electroencephalogram was consistent with complex partial status epilepticus. The subject's final diagnosis was epilepsy. The subject was treated anti-epileptics. The event resolved after two days, and the subject was discharged from the hospital.

6.2.3 Comments and Conclusions
The formulation of DTaP-IPV used in Study 213503/047 was the same as that of the vaccine intended for U.S. licensure except that it also contained 2-phenoxyethanol (as preservative).

Study 213503/047 provides supportive polio immunogenicity data for the evaluation of KINRIX. Among the subset of subjects primed with three doses of IPV, post-vaccination GMTs and booster response rates for anti-poliovirus type 1, type 2, and type 3 were comparable between the DTaP-IPV and INFANRIX + IPOL groups.

As indicated in Section 5.3, the pertussis, diphtheria, and tetanus immunogenicity data from this study are not being considered by CBER in the evaluation of KINRIX because information submitted on the validation of the assays was not adequate.

Although not required by CBER to support approval of KINRIX, in Study 213503/047, the immune responses to the second dose of MMR_{II} administered concomitantly with either DTaP-IPV or with INFANRIX + IPOL were evaluated. Approximately 99% of subjects were seropositive for measles, mumps, and rubella antibody prior to receipt of the second dose of MMR_{II}. The protocol defined anti-mumps seroprotection as an antibody concentration $\geq$1:28 by neutralization and anti-measles seroprotection as an antibody concentration $\geq$150 mIU/mL by ELISA. CBER does not concur that these levels are indicative of protection as there is no established seroprotective level to mumps and it has not been established that an anti-measles IgG titer corresponding to 150 mIU of the 1st WHO International Standard Preparation of anti-measles serum is protective (E-mail communication from Dr. Steven Rubin, CBER, 11/21/07).

Study 213503/047 provides comparative safety data on 200 subjects who received DTaP-IPV and 200 subjects who received INFANRIX + IPOL following four previous doses of INFANRIX and three previous doses of poliovirus vaccine (either three doses of IPV or two doses of IPV followed by one dose of OPV). Approximately 90% of subjects in both groups had received three previous doses of IPV. The data from this study supplement the larger safety database accrued from Study 213503/048 and are supportive for approval of KINRIX in children 4-6 years of age for the fifth dose of DTaP (following four doses of DTaP using PEDIARIX and/or INFANRIX for the first three doses and INFANRIX for the fourth dose) and for the fourth dose of IPV. The protocol-defined endpoints were clear and appropriate. Review of the data did not identify any concerns with trial implementation. The quality of the data appeared to be adequate. With regard to solicited local and systemic adverse events, the safety profile of DTaP-IPV appeared to be comparable to that of separately administered INFANRIX + IPOL. The timing and nature of the serious adverse events reported in this study did not raise concerns about the safety of KINRIX.

6.3 Supportive Trial #2

6.3.1 Applicant's Protocol # and Protocol Title
Study 213503 (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 coadministered with GSK Biologicals' MMR vaccine (Priorix™)

6.3.1.1 Objective/Rationale
This study was conducted to assess the safety and immunogenicity of DTaP-IPV as compared to DTaP and IPV vaccines administered separately.

6.3.1.2 Design Overview
Open, randomized (1:1), multicenter (3 centers) clinical study with two parallel groups of 181 subjects each (DTaP-IPV and INFANRIX + IPOL).

6.3.1.3 Population
The study was conducted in Australia.

Main criteria for inclusion
Healthy children 4 to 6 years of age who had previously received 3 doses of DTaP and polio vaccines at 2, 4, 6 months of age, and a fourth dose of DTaP in the second year of life according to local guidelines. Subjects were also to have had MMR vaccination in the second year of life. Subjects were to have had no previous or intercurrent diphtheria, tetanus, pertussis, or polio disease, and no known exposure to measles, mumps or rubella within 30 days of visit 1.

6.3.1.4 Products Mandated by the Protocol
GSK Biologicals' DTaP-IPV vaccine was administered by deep intramuscular injection into the left deltoid muscle. The formulation of DTaP-IPV was the same as that of KINRIX used in Study 213503/048 (Section 6.1.1.4) with the exception that it also contained ≤2.5 mg of 2-phenoxyenthanol per dose. DTaP-IPV lot 20787A9 was used in Study 213503/046.

The active ingredients of INFANRIX and IPOL are listed in Section 6.1.1.4.

GSK Biologicals' MMR vaccine (Priorix™) (not licensed in the U.S.) contains:
Schwarz measles strain $\geq 10^{3.0}$ $TCID_{50}$
RIT 4385 mumps strain $\geq 10^{3.7}$ $TCID_{50}$
RA 27/3 rubella strain $\geq 10^{3.0}$ $TCID_{50}$

6.3.1.5 Safety Endpoints
- Injection site pain, redness, and swelling; fever, irritability/fussiness, drowsiness, and loss of appetite occurring on the day of vaccination and during the subsequent 14 days.
- General symptoms that may be associated with MMR vaccination (rash/exanthema, suspected signs of meningism including febrile convulsions and parotid/salivary gland swelling) occurring on the day of vaccination and during the subsequent 14 days.
- Unsolicited adverse events through Day 30 post-vaccination.

6.3.1.6 Safety Surveillance/Monitoring
Diary cards were provided for recording solicited local and general adverse events on the day of vaccination and for the next 14 days. Diary cards were reviewed with the subjects' parent/guardian at the post-vaccination visit one month after vaccination. In addition, parents/guardians were instructed to contact the investigator immediately about any condition or event that raised their concern and for large swelling reactions (defined as swelling with a diameter >50 mm, noticeable diffuse swelling or noticeable increase of limb circumference).

6.3.1.7 Statistical Considerations

The planned enrollment was 424 subjects (212 per group).

Due to the inclusion of 22 subjects in the vaccinated cohort who were primed with whole-cell DTP vaccine instead of DTaP, the ATP safety cohort was selected as the primary safety cohort.

The ATP Cohort for Safety included all subjects:
• who had received the doses of study vaccines according to their random assignment, and
• who had sufficient data to perform an analysis of safety (symptom sheet available), and
• for whom administration site of study vaccine/comparator was known, and
• who had not received a vaccine forbidden or not specified in the protocol.

Safety analyses were descriptive. Percentages of particular events and 95% confidence intervals were computed by vaccine group.

6.3.2 Results

6.3.2.1 Populations Enrolled/Analyzed

6.3.2.1.1 Study Sites and Study Period

The study period was 5/27/02 through 1/15/03. Subjects were enrolled from three sites in Australia.

6.3.2.1.2 Subject Disposition and Follow-up

A total of 362 subjects (181 per group) were vaccinated. Of these, 360 subjects (180 per group) completed the study. Two subjects were withdrawn from the study by the parent/guardian after Visit 1. Neither withdrawal was due to an adverse event.

The ATP safety cohort consisted of 338 subjects (DTaP-IPV + MMR Group = 171; DTaP + IPV + MMR Group = 167). Twenty-two subjects in the vaccinated cohort who were primed with whole cell DTP instead of DTaP were not included in the ATP safety cohort.

6.3.2.1.3 Subject Demographics

Subjects ranged in age from 4 to 5 years with a mean age of 4.0 years in both groups. There were 184 females and 145 males, overall. The ratios of females to males were similar between the two groups. The majority of subjects (97.6%) in both groups were Caucasian.

6.3.2.2 Safety Outcomes

In Study 213503/046, the incidence and severity of solicited symptoms appeared similar between groups (confidence intervals overlapped for the incidence of each solicited symptom and for each grade 3 solicited symptom). "Large injection site swelling" (swelling with a diameter >50 mm, noticeable diffuse swelling or noticeable increase of limb circumference) at the DTaP site over the entire study period was reported in 42 (24.6%) of DTaP-IPV subjects and in 49 (29.3%) of INFANRIX + IPOL subjects. Two subjects (DTaP-IPV vaccinees) reported functional impairment that prevented normal everyday activities. Large swellings occurred within two days post-vaccination and lasted less than 5 days for the majority of cases, and in all cases were resolved at the time of final subject contact.

One subject (in Group INFANRIX + IPOL + MMR) reported a serious adverse event. One day after vaccination, he developed fever (37.6°C) and headache. Three days later the fever increased

to 40°C. On the fourth day after vaccination, the subject developed lethargy, severe headache and loss of appetite. He was hospitalized and a diagnosis of significant fever without infective focus was made. The subject was discharged the same day. Five days later, he was seen for persistent fever and was diagnosed with bronchitis and was treated with antibiotics. The child had recovered by 15 days after vaccination.

6.3.3 Comments and Conclusions

The study population for 213503/046 included subjects previously primed with both whole cell DTP and acellular pertussis vaccines, as well as multiple types of acellular pertussis vaccines, and subjects previously primed with three doses of OPV or a sequential schedule of IPV followed by OPV. A non-U.S. licensed MMR vaccine was administered concomitantly with DTaP-IPV or Control vaccines. Thus, CBER considered the immunogenicity data from this study (not included in the BLA) to be of limited relevance to the evaluation of KINRIX for licensure in the U.S. The safety data from this study were considered supportive for the evaluation of KINRIX, and as agreed upon between CBER and the applicant, were submitted in a synopsis format.

Review of the safety synopsis from Study 213503/046 did not cast doubt on the safety of KINRIX as assessed in the pivotal study, Study 213503/048.

7 Overview of Immunogenicity Across Trials

There was only one pivotal study for the evaluation of the immune responses to KINRIX. The immunogenicity data from this study, Study 213503/048, are discussed in Section 6.1.3.2 of this review.

7.1 Immunogenicity Conclusions

The immunogenicity data from Study 213503/048 support the approval of KINRIX in children 4-6 years of age for the fifth dose of DTaP (following four previous doses using PEDIARIX and/or INFANRIX for the first three doses and INFANRIX for the fourth dose) and for the fourth dose of IPV. In Study 213503/048, the immunogenicity of KINRIX was evaluated in subjects concomitantly administered the second dose of U.S. licensed MMR. For further discussion, see Section 6.1.3 and Section 6.1.3.2.

Study 213503/048, the pivotal study of KINRIX, was initiated and the active phase nearly completed, prior to the June 2006 ACIP recommendation for routine administration of a second dose of varicella vaccine in children ages 4-6 years. Thus, the KINRIX BLA does not contain data on the immune response to KINRIX administered concomitantly with varicella vaccine. The applicant has proposed to conduct a study post-licensure to evaluate the immunogenicity and safety of KINRIX administered concomitantly with varicella vaccine (see Section 11.2).

8 Overview of Safety Across Trials

The safety of KINRIX was evaluated in one pivotal study, Study 213503/048. This study accounted for 89% of the overall safety database. The safety data from this study are discussed in Section 6.1.3.3. The two supportive studies did not cast doubt on the conclusions regarding the safety of KINRIX based on the pivotal study. Thus, a full overview of safety across trials will not be presented in this review.

8.1 Overall Safety Database

A total of 3,537 subjects 4-6 years of age received a single dose of GSK Biologicals' DTaP-IPV vaccine in three clinical studies (see Table 2 Section 5.2). Of these subjects, 3,156 (89%) received KINRIX in the pivotal study, Study 213503/048. The other two studies provided

supportive safety data. In the pivotal study and in one of the supportive studies, GSK Biologicals' DTaP-IPV was administered concomitantly with U.S. licensed MMR vaccine.

In addition to the safety database from clinical trials, post-marketing safety data were provided on GSK Biologicals' DTaP-IPV vaccine, reflecting distribution of approximately---------- doses outside of the U.S. during a period of approximately 10 years (Section 5.1.2.1).

8.2 Safety Conclusions

The safety data in the BLA support the approval of KINRIX in children 4-6 years of age for the fifth dose of DTaP (following four previous doses using PEDIARIX and/or INFANRIX for the first three doses and INFANRIX for the fourth dose) and for the fourth dose of IPV. For further discussion, see Section 6.1.3 and Section 6.1.3.3.

The studies included in the BLA were initiated prior to the June 2006 ACIP recommendation for routine administration of a second dose of varicella vaccine in children ages 4-6 years. Thus, the KINRIX BLA does not contain safety data on KINRIX administered concomitantly with varicella vaccine. The applicant has proposed to conduct a study post-licensure to evaluate the immunogenicity and safety of KINRIX administered concomitantly with varicella vaccine (see Section 11.2).

9 Additional Clinical Issues

9.1 Directions For Use

The proposed directions for use [resuspension with vigorous shaking, intramuscular injection (upper deltoid preferred), and refrigerated storage between 2° and 8°C] are consistent with use in the clinical trials.

9.2 Dose Regimen

The proposed dose regimen for KINRIX is a single 0.5-mL dose by intramuscular injection in children 4 through 6 years of age (prior to the seventh birthday) as the fifth dose in the DTaP series and the fourth dose in the IPV series.

The available data support use of KINRIX as a single dose in children 4 through 6 years of age as the fifth dose in the DTaP series in children who received four previous doses of INFANRIX and as the fourth dose in the IPV series. Because the DTaP component of PEDIARIX is the same as that of INFANRIX and KINRIX, the data also support use of KINRIX in children whose DTaP vaccination series has been with three doses of PEDIARIX and/or INFANRIX followed by a fourth dose with INFANRIX. The available data do not support the use of KINRIX in children who have previously received DTaP vaccines from different manufacturers.

9.3 Special Populations: Pediatrics

GSK Biologicals requested a waiver of pediatric studies of KINRIX for children 0-4 years of age and 7-18 years of age. As clinical reviewer for the KINRIX BLA, I recommend waivers for studies of KINRIX in the pediatric population 0-<4 years of age and 7-18 years of age. The justification for recommending waivers of studies of KINRIX in these age groups, as outlined below, was presented to FDA's Pediatric Review Committee. In their meeting of 1/23/08, the Committee concurred with the recommendations and justification for granting partial waivers of pediatric studies of KINRIX in these age groups.

<u>0-6 weeks</u>

The justification for waiver of studies of KINRIX in children 0-6 weeks of age is based on the following sections of the Pediatric Research Equity Act of 2007:

> Section 505B(a)(4)(B)(i): necessary studies are impossible or highly impracticable
>
> Section 505B(a)(4)(B)(iii): the drug or biological product—(I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group; and (II) is not likely to be used by a substantial number of pediatric patients in that age group.

Necessary studies are impossible or highly impracticable

It would be difficult to enroll sufficient numbers of subjects 0-6 weeks of age in studies of KINRIX and inappropriate to require such studies because of:

- the lack of apparent benefit of administration of diphtheria toxoid, tetanus toxoid, and poliovirus vaccine to infants <6 weeks of age, compared with vaccination beginning at 6 weeks of age;
- the potential for immune suppression to subsequent vaccination that may be associated with early-life vaccination;
- the potential for clinically significant fever and other adverse events that may be associated with vaccination of vulnerable neonates.

With the exception of Hepatitis B vaccine, which is routinely administered shortly after birth, in part, to prevent unrecognized perinatal transmission of hepatitis B virus, the infant immunization program in the U.S. is initiated at a minimum of 6 weeks of age. In general, limitations of the neonatal immune response (e.g., weak and short-lived antibody response and inhibitory influence of maternal antibodies) have been significant barriers to effective immunization earlier in life.

Among the diseases targeted for prevention by KINRIX (diphtheria, tetanus, pertussis, and poliomyelitis), only pertussis occurs in U.S. infants who are too young to be protected as a result of vaccination beginning at 6 weeks of age. Whereas earlier immunity to pertussis would be beneficial, it is not clear that this could be achieved with earlier vaccination with existing vaccines. Furthermore, with regard to KINRIX, there is no clear potential benefit to earlier administration of diphtheria toxoid, tetanus toxoid, and poliovirus vaccine. In fact, clinical data from one published study suggest that administration of Diphtheria and Tetanus Toxoid (DT) to newborn infants may be associated with suppression of antibody responses to subsequently administered diphtheria toxoid and *Haemophilus influenzae* type b conjugate vaccines.(2)

As with all preventive vaccines, a high standard of safety would be expected for vaccines administered to healthy neonates. Moreover, the vulnerability of the neonate poses unique safety considerations for clinical studies of preventive vaccines. For example, post-vaccination fever assumes greater clinical significance in neonates than in older infants or children because of the high risk for serious bacterial infection and the difficulty in predicting the presence of invasive disease by physical exam and laboratory testing in the neonatal period. Hospitalization, diagnostic evaluation including cerebrospinal fluid studies, and administration of intravenous antibiotics represent the standard of care in the U.S. for febrile neonates.

Administration of KINRIX in infants 0-6 weeks of age poses at least a theoretical concern for excess fever due to vaccination. Fever in older infants has been reported relatively commonly following administration of some DTaP vaccines and DTaP based combination vaccines. For example, in clinical studies, fever $\geq$100.4^{o}F within four days post-vaccination was reported in approximately 25% of 2-month old infants who received PEDIARIX, a combination vaccine that

contains the same DTaP and IPV components as KINRIX.(3) Observed rates of fever ≥100.4°F, fever >102.2°F, and medically attended fever within four days post-vaccination at age 2 months have been statistically significantly higher following PEDIARIX compared with separately administered DTaP, IPV, and Hepatitis B vaccine.(3)

KINRIX does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used by a substantial number of infants 0-6 weeks of age

For the prevention of diphtheria, tetanus, and poliomyelitis, KINRIX administered in infants 0-6 weeks of age does not represent a meaningful therapeutic benefit over existing vaccines that are routinely administered beginning at a minimum of 6 weeks of age. In view of the potential risks of neonatal vaccination and the lack of added benefit to earlier vaccination against diphtheria, tetanus, and poliomyelitis, KINRIX is not likely to be used by a substantial number of infants 0-6 weeks of age.

6 weeks-<4 years

The justification for waiver of studies of KINRIX in children 6 weeks through <4 years of age is based on the following section of the Pediatric Research Equity Act of 2007:

> Section 505B(a)(4)(B)(iii): the drug or biological product—(I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group; and (II) is not likely to be used by a substantial number of pediatric patients in that age group.

KINRIX does not represent a meaningful therapeutic benefit over existing therapies for children 6 weeks through <4 years of age

For the age group 6 weeks through <4 years, the U.S. market is currently well supplied for DTaP and IPV vaccines and vaccination coverage rates are high. In the U.S., there are currently three DTaP vaccines (INFANRIX, DAPTACEL, and Tripedia) and one DTaP-based combination vaccine, PEDIARIX, licensed for use in children 6 weeks through 6 years of age. In the age group under consideration (i.e., 6 weeks-<4 years), the three available DTaP vaccines are routinely administered at 2, 4, 6, and 15-18 months of age. PEDIARIX is approved for the first three doses of the DTaP series. Based on data from the National Immunization Survey, by the time U.S. children are 3 years of age, an estimated 86% have received four doses of DTaP.(4)

For the age group 6 weeks through <4 years, there is currently one IPV vaccine (IPOL) and one combination vaccine containing IPV (PEDIARIX) licensed and distributed in the U.S. In the age group under consideration, three doses of IPV are recommended at 2, 4, and 6-18 months of age. By the time U.S. children are 3 years of age, an estimated 92% have received at least three doses of poliovirus vaccine.(4)

KINIRX is not likely to be used by a substantial number of children 6 weeks-<4 years of age

Use of KINRIX at 2, 4, and 6 months of age would require one additional injection at each visit over the number of injections required using PEDIARIX. According to the applicant, PEDIARIX (also manufactured by GlaxoSmithKline Biologicals) has approximately ------- of the U.S. market share among DTaP vaccines for the first three doses of the recommended series.

Use of KINRIX at 15-18 months of age would be limited because most children in this age group do not need a dose of IPV. The applicant indicated that 79% of patient claim based polio vaccine administrations in the first two years of life occur by age 7 months, suggesting that most children receive the third dose of IPV by 7 months of age.

7-18 years

The justification for waiver of studies of KINRIX in children and adolescents 7-18 years of age is based on the following sections of the Pediatric Research Equity Act of 2007:

> Section 505B(a)(4)(B)(i): necessary studies are impossible or highly impracticable
>
> Section 505B(a)(4)(B)(iii): the drug or biological product—(I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group; and (II) is not likely to be used by a substantial number of pediatric patients in that age group.

Necessary studies are impossible or highly impracticable

Because of the following considerations, it would not be feasible to conduct studies of KINRIX in children and adolescents 7-18 years of age, and inappropriate to require such studies.

- A fifth dose of DTaP and a fourth dose of IPV, routinely administered prior to school entry at age 4-6 years, completes the routinely recommended series for these vaccines.

- A single dose of dose of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap) is routinely recommended at 11-12 years of age. For adolescents 11-18 years of age, two Tdap vaccines, ADACEL and BOOSTRIX, are licensed and distributed in the U.S. BOOSTRIX is also approved for use in children 10 years of age. Both available Tdap vaccines were specifically formulated to contain lower amounts of diphtheria toxoid than DTaP vaccines to reduce the potential for reactogenicity that may be associated with booster vaccination.

- With regard to the age group 7-9 years, for which there are no licensed pertussis vaccines in the U.S., a very small number of children, geographically dispersed, would be expected to need vaccination against diphtheria, tetanus, pertussis, and poliomyelitis. Furthermore, IPOL and three Td vaccines (Tetanus and Diphtheria Toxoids Adsorbed for Adult Use) are licensed for use in children 7-9 years of age, although few children in this age group are in need of these vaccines. Thus, studies to evaluate KINRIX in children 7-9 years of age would be highly impracticable.

KINRIX does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used by a substantial number of children and adolescents 7-18 years of age

For children and adolescents 10-18 years of age, KINRIX does not represent a meaningful therapeutic benefit over Tdap. There are also three Td vaccines approved for use in children and adolescents 7-18 years of age. Although there are no recommendations for routine use of IPV in children and adolescents 7-18 years of age, IPOL is approved for use in this age group. Vaccination with KINRIX at 7-9 years of age (no available pertussis vaccine for this age group) does not represent a meaningful therapeutic benefit over the current schedule of routine DTaP vaccination at 4-6 years of age and routine Tdap vaccination at 11-12 years of age.

Given the availability of Tdap vaccines that have a lower amount of diphtheria toxoid relative to KINRIX, it is unlikely that KINRIX would be used by a substantial number of children and adolescents 7-18 years of age. With regard to the age group 7-9 years, for which Tdap vaccines are not approved, very few U.S. children would be expected to need vaccination against the diseases targeted by KINRIX. If there was a need to study a preventive vaccine for diphtheria, tetanus, and pertussis in this age group, Tdap vaccines would be preferable over KINRIX because of their lower diphtheria toxoid content.

10 Conclusions—Overall

The available safety and immunogenicity data support the approval of KINRIX administered as a single dose in children 4-6 years of age for:

- the fifth dose of DTaP following
  - PEDIARIX and/or INFANRIX for the first three DTaP doses and INFANRIX for the fourth dose, and
- the fourth dose of IPV.

11 Recommendations

11.1 Approval Recommendation

KINRIX is recommended for approval for a single dose in children 4-6 years of age for active immunization against diphtheria, tetanus, pertussis, and poliomyelitis as:

- the fifth dose of DTaP following
  - PEDIARIX and/or INFANRIX for the first three DTaP doses and INFANRIX for the fourth dose, and
- the fourth dose of IPV.

11.2 Recommendations on Postmarketing Actions

Following discussions with CBER, the applicant committed to conduct a randomized, open label, comparative study evaluating safety and immunogenicity of KINRIX when given concomitantly with varicella vaccine. The study will be conducted in approximately 400 children 4-6 years of age who had received 4 doses of DTaP-containing vaccine (INFANRIX or PEDIARIX) and 3 doses of IPV-containing vaccine (IPOL or PEDIARIX) in the first 2 years of life, and 1 dose of MMR and varicella vaccines (separately or in a combination vaccine) in the second year of life. Subjects will be randomized to receive vaccination with KINRIX, MMR and varicella vaccine at their first study visit, or with KINRIX and MMR at their first study visit, followed by varicella vaccine at their second study visit. A safety follow-up contact will be completed for all subjects approximately 6 months following vaccination with KINRIX. The final study protocol will be submitted by 8/30/08. The study will be initiated no later than 1/30/09. The final study report will be submitted by 7/31/11.

The applicant has proposed to continue close monitoring of all worldwide spontaneously reported large injections site swelling reactions. Efforts will include use of a questionnaire to obtain a more standardized and detailed description of the cases.

The applicant has proposed enhanced passive surveillance of stroke, hypercoagulable state, thrombus, and thromboembolism, to further evaluate any possible association between their DTaP-IPV vaccine and these events. All spontaneous reports of cerebrovascular accident and related events will be expedited to FDA.

The primary review of GSK Biologicals' pharmacovigilance plan for KINRIX, including monitoring of large injection site swelling reactions, stroke and related diagnoses is being conducted by Dr. Soju Chang, Division of Epidemiology, Office of Biostatistics and Epidemiology.

11.3 Recommendations on Request for Partial Waiver of Pediatric Studies

See Section 9.3 regarding recommendations for waiver of studies of KINRIX in pediatric populations 0-<4 years and 7-18 years.

12 Labeling

The package insert submitted by the applicant was in the format required by FDA's Final Rule titled "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" published in January 2006. The discussion in Section 9.2 of this review regarding previous DTaP vaccination history and use of KINRIX is relevant to the Highlights, Indications and Usage, and Dosage and Administration sections of the package insert. Specifically, these sections of the package insert should clearly define the subpopulation for which KINRIX is indicated as children 4-6 years of age whose previous DTaP vaccination history has consisted of the first three doses with INFANRIX and/or PEDIARIX and the fourth dose with INFANRIX and who previously received three doses of IPV. No other major labeling issues have been identified.

13 References

1. Lynch JK. Cerebrovascular disorders in children. Curr Neurol Neurosci Rep 2004;4:129-138.

2. Lieberman JM, Greenberg DP, Wong VK, et. al. Effect of neonatal immunization with diphtheria and tetanus toxoids on antibody responses to *Haemophilus influenzae* type b conjugate vaccines. J Pediatr 1995;126:198-205.

3. PEDIARIX Prescribing Information.

4. CDC. National, state, and urban area vaccination coverage among children aged 19-35 months – United States, 2004. *MMWR Weekly* 2005;54(29):717-721.