18 October 2018
EMA/765993/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Infanrix hexa

diphtheria (d), tetanus (t), pertussis (acellular, component) (pa), hepatitis b (rdna) (hbv), poliomyelitis (inactivated) (ipv) and haemophilus influenzae type b (hib) conjugate vaccine (adsorbed)

Procedure no: EMEA/H/C/000296/P46/130

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Date of this report:	24/09/2018
Deadline for comments:	08/10/2018

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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Administrative information

Name of the Rapporteur	**Name Bart Van der Schueren**
Rapporteur contact person:	**Name: Annick Dujardin** Email:annick.dujardin@afmps.be
Names of the Rapporteur's assessors	**Name Didier Hue** Email:Didier.Hue@afmps.be **Name Nele Berthels**
Name of the EMA contact:	**Name Viktor Vlcek** Email:viktor.vlcek@ema.europa.eu

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1. Introduction

This report covers the following post-authorisation commitments undertaken by the MAH:

A stand-alone submission of the final study report for the DTPa-HBV-IPV-135 study, in accordance with Article 46 of Regulation (EC) No 1901/2006. The DTPa-HBV-IPV-135 study is a Phase III, randomized, open-label, controlled, multicenter study to evaluate immunogenicity and safety of GlaxoSmithKline (GSK) Biologicals' *Infanrix hexa* vaccine when administered to healthy infants as primary vaccination at 2, 4 and 6 months of age, co-administered with Prevnar and *Rotarix* with a booster dose of GSK Biologicals' *Infanrix* and *Hiberix* vaccines at 15-18 months of age. The study DTPa-HBV-IPV-135 was conducted in the United States of America.

The present study 117119 (DTPA-HBV-IPV-135) was intended to generate pivotal immunogenicity data demonstrating non-inferiority of the immune responses against pertussis antigens of *Infanrix hexa* compared to *Pediarix*, which is currently one of the DTaP combination vaccines widely used as a standard of care in the US. Additionally, this study was to also provide descriptive data with regard to the immunogenicity of the other vaccine antigens and the safety profile in US subjects. These pivotal immunogenicity non-inferiority data for pertussis and descriptive safety data were intended to support the registration of GSK Biologicals' combined DTPa-HBV-IPV/Hib (*Infanrix hexa*) vaccine in the US. A subsequent Phase III study was planned to provide pivotal data regarding lot-to-lot consistency, safety and the immunogenicity of the other vaccine antigens.

Comparison of immunogenicity data from separate clinical studies for *Infanrix hexa* and *Pentacel*, given on a 2-4-6 month schedule, suggests that the immune response to the Hib component of these vaccines is similar. This study was to provide descriptive information regarding the immune response to the Hib components of *Infanrix hexa* and *Pentacel* following a 3-dose primary series, prior to further evaluation in Phase III studies.

1.1. Steps taken for the assessment

Submission date:	02/08/2018
Start of procedure:	20/08/2018
CHMP Rapporteur's preliminary assessment report circulated on:	24/09/2018
CHMP Rapporteur's updated assessment report circulated on:	11/10/2018
CHMP opinion:	18/10/2018

2. Assessment of the post-authorisation measure PAM

Objectives:

Primary: Epoch 001 (Primary vaccination):

- To demonstrate the non-inferiority of *Infanrix hexa* to *Pediarix* co-administered with *ActHIB*, in terms of antibody geometric mean concentrations (GMCs) for pertussis antigens [pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN)] one month after the third dose of the primary vaccination.

  Criteria for non-inferiority: Non-inferiority in terms of immune response to pertussis antigens was to be demonstrated if, for each of the three antigens, the upper limit (UL) of the 95% confidence interval (CI) on the GMC ratio [Pedia divided by Hexa] was ≤ 1.5.

Secondary: Epoch 001 (Primary vaccination)

- To assess the immune response to *Infanrix hexa, Pediarix*, *ActHIB, Pentacel* and *Engerix-B*, in terms of seroprotection status, seropositivity status and concentrations or titers of antibodies to D (Diphtheria), T (Tetanus), HBs (Hepatitis B surface antigen), pertussis, poliovirus types 1, 2 and 3 and PRP (Polyribosyl-Ribitol- Phosphate) antigens, one month after the third dose of the primary vaccination.
- To assess the safety and reactogenicity of a 3-dose primary vaccination course of *Infanrix hexa,* of *Pentacel* coadministered with *Engerix-B,* and that of *Pediarix* co-administered with *ActHIB,* in terms of solicited local symptoms.
- To assess the safety and reactogenicity of all study vaccines in terms of solicited general events, unsolicited adverse events, new-onset chronic illnesses (NOCIs; referred to as new-onset chronic diseases (NOCDs) in the protocol) and serious adverse events.

Secondary: Epoch 002 (Booster vaccination)

- To assess the immunogenicity of *Infanrix hexa, Pentacel, Engerix-B, Pediarix* and *ActHIB*, in terms of persistence of the antibodies to D, T, pertussis, HBs, poliovirus types 1, 2 and 3 and PRP antigens, before the booster dose.
- To assess the immune response to *Infanrix, Hiberix*, *ActHIB* and *Pentacel,* in terms of seroprotection status, seropositivity status and antibody concentrations or titers for D, T, pertussis and PRP antigens, and in terms of booster response for pertussis antigens following *Infanrix* and *Pentacel*, one month after the booster dose.
- To assess the safety and reactogenicity of booster doses of *Infanrix, Hiberix*, *ActHIB* and *Pentacel.*

Methodology:

- Experimental design: Phase III, open-label, randomized, controlled, multi-centric, single-country study with five parallel groups.
  - Epoch 001: Primary, starting at Visit 1 (Day 0) and ending at safety follow up contact (i.e. six months following the third dose, Month 10);
  - Epoch 002: Booster, starting at Visit 5 (Month 13-16) and ending at Visit 6 (Month 14-17).
- Control: active controls.
  - Epoch 001: *Pediarix* + *ActHIB* and *Pentacel* + *Engerix-B*;
  - Epoch 002: *Infanrix* + *ActHIB* and *Pentacel*.

Vaccination schedules:

Epoch 001

- Hexa Group: Subjects in this group were to receive three doses of *Infanrix hexa* (lot A, lot B or lot C as per the group allocation) co-administered with *Prevnar13* at 2, 4 and 6 months of age and *Rotarix* at 2 and 4 months of age.

    ☐ Hexa_1 Group: Subjects were to receive lot A of *Infanrix hexa*;

    ☐ Hexa_2 Group: Subjects were to receive lot B of *Infanrix hexa*;

    ☐ Hexa_3 Group: Subjects were to receive lot C of *Infanrix hexa*.

- Pedia Group: Subjects in this group were to receive three doses of *Pediarix* and *ActHIB* co-administered with *Prevnar13* at 2, 4 and 6 months of age and *Rotarix* at 2 and 4 months of age.

- Penta Group: Subjects in this group were to receive three doses of *Pentacel* and *Engerix-B** co-administered with *Prevnar13* at 2, 4 and 6 months of age and *Rotarix* at 2 and 4 months of age.

*Subjects in the Penta Group who received a dose of hepatitis B vaccine from birth up to 30 days prior to study vaccination were not to receive *Engerix-B* at 4 months of age (Visit 2).

Epoch 002

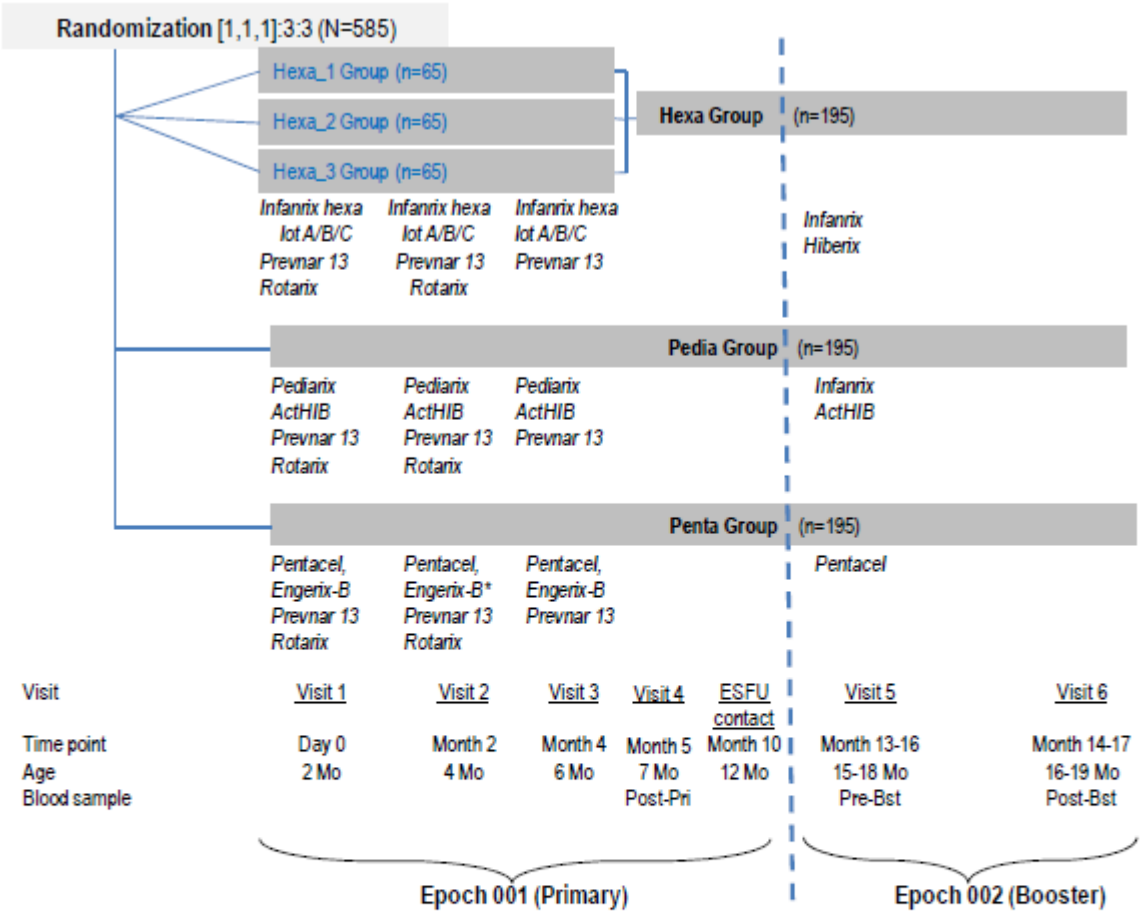
- Hexa Group: Subjects were to receive a booster dose of *Infanrix* and *Hiberix* vaccines at 15-18 months of age.

- Pedia Group: Subjects were to receive a booster dose of *Infanrix* and *ActHIB* vaccines at 15-18 months of age.

- Penta Group: Subjects were to receive a booster dose of *Pentacel* vaccine at 15-18 months of age.

The fourth dose of pneumococcal conjugate vaccine is recommended to be administered at approximately 12-15 months of age. Since the booster dose of the candidate vaccine/active controls were given in this study at 15-18 months of age, the fourth dose of *Prevnar13* was not to be administered as part of the study protocol. Subject's parent(s)/Legally Acceptable Representative(s) (LARs) were to be reminded at Visit 3 and Visit 4 to consult their primary health care provider regarding the fourth dose of *Prevnar13* at 12-15 months for their child.

As the analyses were to be performed regardless of the lot of *Infanrix hexa* received, unless otherwise specified, the Hexa_1, Hexa_2 and Hexa_3 groups were pooled together for the analysis and were called the Hexa group.



N = number of subjects in the study; n = number of subjects in each group; Mo = months
Visit 3 should be conducted at least 8 weeks after Visit 2, with subjects at least 24 weeks of age, in order to comply with US recommendations on hepatitis B dosing
Post-Pri = blood sample collected from subjects, one month after the administration of the third dose in the Epoch 001
Pre-Bst = blood sample collected from subjects, before the administration of the booster dose in the Epoch 002
Post-Bst = blood sample collected from subjects, one month after the administration of booster dose in the Epoch 002
* *Engerix-B* should not be given at Month 2 (4 months of age) if a dose of hepatitis B vaccine was given at birth up to 30 days prior to study dose 1 to the subject in the Penta Group
ESFU = Extended safety follow-up

Table 1 Study groups and epochs foreseen in the study

Study groups	Number of subjects	Age (Min/Max) at Visit 1	Epochs	
			Epoch 001	Epoch 002
Hexa_1	65	6 weeks -12 weeks	x	x
Hexa_2	65	6 weeks -12 weeks	x	x
Hexa_3	65	6 weeks -12 weeks	x	x
Pedia	195	6 weeks -12 weeks	x	x
Penta	195	6 weeks -12 weeks	x	x

The study groups and treatment foreseen in the study are presented in Table 2.

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Groups				
		Hexa_1	Hexa_2	Hexa_3	Pedia	Penta
Epoch 001						
Infanrix hexa		x	x	x		
	Hib					
Pediarix					x	
ActHIB	ActHIB				x	
	NaCl					
Pentacel	DTaP-IPV (Sanofi Pasteur)					x
	ActHIB					
Engerix-B *	HBV					x
Prevnar13	Prevenar 13	x	x	x	x	x
Rotarix	HRV	x	x	x	x	x
	$CaCO_3$					
Epoch 002						
Infanrix	DTPa	x	x	x	x	
Hiberix	Hib	x	x	x		
	NaCl					
ActHIB	ActHIB				x	
	NaCl					
Pentacel	DTaP-IPV (Sanofi Pasteur)					x
	ActHIB					

* *Engerix-B* should not be given at Month 2 (4 months of age) if a dose of hepatitis B vaccine was given at birth up to 30 days prior to study dose 1 to the subject in the Penta Group.

Study Population:

Healthy male and female infants, between and including, 6 and 12 weeks of age at the time of the first dose who were free of obvious health problems, born full-term after a gestation period of 37 weeks to less than 42 completed weeks and who had not received vaccination against diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b, rotavirus, pneumococcus, and/or poliovirus; or more than one previous dose of hepatitis B vaccine administered at least 30 days prior to enrolment. Written informed consent was obtained from the parent/guardian of the subject prior to any study-related activity.

RESULTS Summary:

Immunogenicity results: Primary Vaccination Epoch

The primary objective to demonstrate the non-inferiority of *Infanrix hexa* to *Pediarix* co-administered with *ActHIB*, in terms of antibody GMCs for pertussis antigens (PT, FHA and PRN) one month after the third dose of the primary vaccination was reached:

For PT, FHA and PRN, the upper limit of the 95% CI for the GMC ratio [Pedia group divided by Hexa group] was ≤ 1.5: For anti-PT antibody - 1.31; for anti-FHA antibody – 1.35; for anti-PRN antibody – 0.99 (Synopsis Table 2).

Anti-Diphtheria and anti-Tetanus antibody responses: All subjects had anti-D antibody concentrations ≥ 0.1 IU/mL and at least 99.3% of subjects had anti-T antibody concentrations ≥ 0.1 IU/mL, indicating seroprotection against these diseases (Synopsis Table 4).

Anti-Polio 1, 2, and 3 antibody responses: At least 99.3% of subjects had anti-Polio 1 antibody titer ≥8, all subjects had anti-Polio 2 antibody titer ≥8 and at least 98.4% of subjects had anti-Polio 3 antibody titer ≥8 (Synopsis Table 5).

Anti-PRP antibody responses: Short-term seroprotection against *Haemophilus influenzae* type b disease (anti-PRP antibody concentrations ≥ 0.15 µg/mL) was met by at least 94.8% across groups using the fully validated assay (Synopsis Table 6).

Anti-HBs antibody responses: Seroprotection against Hepatitis B virus (HBV) disease (anti-HBs ≥ 10 mIU/mL) was reached by at least 97.8% of subjects across the groups (Synopsis Table 7).

Immunogenicity results: Booster Vaccination Epoch

The proportion of subjects with an anti-Pertussis antibody booster response was: For anti-PT antibody: ≥93.1% across groups; for anti-FHA antibody: ≥ 97.7% across groups; for anti-PRN antibody: ≥ 97.4% across groups.

Anti-D and Anti-T immune response: Seroprotection (≥ 0.1 IU/mL) was reached for at least 99.2% of subjects across groups and long-term seroprotection (antibody concentrations ≥1.0 IU/mL) was reached by all subjects for anti-D and for anti-T antibody by between 97.8-100% of subjects (Synopsis Table 10).

Anti-PRP immune response: Short-term seroprotection (≥ 0.15 µg/mL): Between 98.5-100% of subjects across groups and long-term seroprotection (≥ 1.0 µg/mL) for between 97.7-99.3% of subjects across groups.

Safety results : Primary Total vaccinated cohort - Safety summary

Any Symptom: In all three groups (Hexa, Pedia and Penta) over the primary doses, symptoms (solicited and/or unsolicited, local and/or general) were reported for 93.4-96.4% of subjects.

Solicited local symptoms: Pain was the most frequently reported solicited local symptom reported in 67.9% of subjects in the Hexa group, in 82.0% of subjects in the Pedia group and in 79.8% of subjects in the Penta group.

Pain was also the most frequently reported Grade 3 solicited local symptom reported in 4.3% of subjects in the Hexa group, 18.0% of subjects in the Pedia group and 11.7% of subjects in the Penta group.

Solicited general symptoms: Irritability / Fussiness was the most frequently reported solicited general symptom in all groups, reported in 87.7% of subjects in the Hexa group, in 96.3% of subjects in the Pedia group and in 94.1% of subjects in the Penta group overall. Irritability was also the most commonly reported grade 3 solicited general symptom, reported for 9.6% of subjects in the Hexa group, 18.5% of subjects in the Pedia group and 16.0% of subjects in the Penta group overall.

Unsolicited adverse events: At least one unsolicited symptom within the 31-day post-vaccination period after each vaccination was reported for 57.9%, 55.7% and 49.0% of subjects in the Hexa, Pedia and Penta groups, respectively. The most commonly reported unsolicited symptom in the three groups was Upper Respiratory Tract Infection (URTI): Hexa group: 15.4%; Pedia group: 11.9%; Penta group: 13.3%. Grade 3 unsolicited symptoms were reported for 6.7%, 6.2% and 3.6% of subjects in Hexa, Pedia and Penta groups, respectively. The most commonly reported grade 3 unsolicited symptoms were: Hexa group: URTI and Otitis media (1.5%); Pedia group: URTI, Conjunctivitis and Irritability (1.0%); Penta group: URTI (1.0%).

Adverse events of interest: New Onset of Chronic Illness (NOCI) symptoms were reported for 7 subjects (3.6%) in the Hexa group, 11 subjects (5.7%) in the Pedia group and 10 subjects (5.1%) in the Penta group. The two reported symptoms in the Hexa group were Dermatitis atopic (2.6%) followed by Bronchial hyperreactivity (1.0%). In the Pedia group, the symptom reported by more than one subject was Dermatitis atopic (3.6%). In the Penta group, the symptoms reported by more than one subject were Dermatitis atopic (3.6%) and Asthma (1.0%).

Serious adverse events: Non-fatal SAEs from Dose 1 up to 6 months following priming doses were reported for 7 (3.6%) subjects in the Hexa group and Penta group, and 1 (0.5%) subject in the Pedia group. All SAE were considered recovered/resolved without sequelae at the end of the study except one non-causally related event of Choking in a 47-week-old female in the Hexa group which was considered recovered/resolved with sequelae.

Three SAEs occurring in two subjects were considered causally related to primary vaccination by the investigator: An SAE of Lethargy in an 8-week-old female subject in the Hexa group which recovered/resolved after one day without sequelae; 2 SAEs in the same subject: one “Apparent life-threatening event” and one event of Leukocytosis were observed in a 10-week-old female subject in the Hexa group which recovered/resolved over 1-2 days without sequelae.

No fatal SAEs were reported during the primary vaccination Epoch of the study.

Withdrawals due to AEs /SAEs: Two subjects had adverse events leading to premature discontinuation during the primary vaccination period: one Hexa group subject with an SAE of Lethargy reported after the first vaccination; one Penta group subject with a Non-Serious Adverse Event of Seizure reported after the Month 2 dose.

Booster Total vaccinated cohort - Safety summary

Any Symptom: At least one solicited or unsolicited symptom was reported during the Booster phase for 77.2% of Hexa group subjects, 81.6% of Pedia group subjects and 70.2% of Penta group subjects.

Solicited local symptoms: Pain was the most frequently reported solicited local symptom reported in 46.8% of subjects in the Hexa group, 51.0% of Pedia group subjects and 39.3% of Penta group subjects. Redness was the most frequently reported Grade 3 solicited local symptom reported in 1.3-5.2% of subjects in the three groups.

Solicited general symptoms: Irritability / Fussiness was the most frequently reported solicited general symptom in all the groups, reported in 56.2% of Hexa group subjects, in 62.7% of Pedia group subjects and in 50.3% of Penta group subjects. Irritability / Fussiness was also the most commonly reported grade 3 solicited general symptom reported for between 2.0 and 2.7% of subjects across groups.

Unsolicited adverse events: At least one unsolicited symptom within the 31-day post-vaccination period after the booster vaccination was recorded for 22.2%, 22.2% and 25.5% of subjects in the Hexa, Pedia and Penta groups, respectively. The most commonly reported unsolicited symptoms were: Hexa group: Pyrexia (3.0%); Pedia group: Pyrexia, Otitis media and URTI (3.2%); Penta group: URTI (5.0%). A grade 3 unsolicited symptom was reported for 3.0%, 1.9% and 1.9% of subjects in Hexa, Pedia and Penta groups, respectively. No grade 3 unsolicited symptom was reported by more than one subject in any group.

Adverse events of interest: NOCI were reported for 4 subjects (2.4%) in the Hexa group, 1 subject (0.6%) in the Pedia group and 1 subject (0.6%) in the Penta group. Only Seasonal allergy symptoms were reported by more than one subject in any group: 3 (1.8%) subjects.

Large injection site reactions up to 4 days (D0-D3) after vaccination: Two subjects (1.3%) in the Hexa group and one subject (0.7%) in the Pedia group had Local Swelling, and Diffuse Swelling was recorded in one subject (0.6%) in the Hexa group.

Serious adverse events within 31 days post booster: Non-fatal SAEs within 31 days post-booster dose were reported for one (0.6%) subject in the Hexa group (Petechiae), for one (0.6%) subject in the Penta group (Seizure like phenomena), and no subject in the Pedia group.

None of the two non-fatal SAEs were considered to be causally-related to vaccination and both were recorded to have an outcome of “recovered/resolved”.

Withdrawals due to AEs /SAEs: No subject was withdrawn due to an AE or SAE during the booster Epoch.

SAEs for the full study: There were no fatal SAEs throughout the study. SAEs were reported for 8 subjects in the Hexa group and Penta group, and for one subject in the Pedia group throughout the study.

Conclusion:

- The primary objective of the study was met: One month post-primary vaccination, *Infanrix hexa* was demonstrated to be non-inferior to *Pediarix+ACTHib* in terms of antibody GMCs for the three pertussis antigens (PT, FHA, and PRN).
- One month after the primary vaccination: The immune responses to *Infanrix hexa, Pediarix+ACTHib* and *Pentacel/Engerix-B* were similar between the different groups, in terms of seroprotection/seropositivity rates and GMCs.

  The lowest anti-PRP GMCs were observed after *Infanrix hexa* vaccination as compared to *Pediarix+ACTHib* and *Pentacel+Engerix-B.*

- One month after the booster vaccination: The immune responses to *Infanrix+Hiberix* (booster vaccines used after *Infanrix hexa* priming), *Infanrix+ActHIB* (booster vaccines used after *Pediarix+ActHIB* priming) and *Pentacel* were similar between the different groups, in terms of seroprotection/seropositivity rates and GMCs.

  Similar Anti-PRP long-term protection antibody levels were observed (≥1.0 μg/mL) between *Infanrix+Hiberix*, *Infanrix+ActHIB* and *Pentacel* after booster vaccination.

- Safety, reactogenicity: Clinically acceptable safety and reactogenicity profile in the different vaccination groups, aligned with the very well-known profiles of the study vaccines.

3. Rapporteur's overall conclusion

The Rapporteur agrees with the conclusions of the Applicant. The safety and immunogenicity results of this study are in line with the approved SmPC for *Infanrix hexa*. No updates are considered necessary.

☒ PAM fulfilled (all commitments fulfilled) - No further action required