Rapporteur's Public Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

Fluarix

DE/W/0054/pdWS/002-005

Marketing Authorisation Holder:

GlaxoSmithKline GmbH & Co. KG

Rapporteur:	**Germany (PEI)**
Finalisation procedure (day 120):	**April 16, 2013**
Date of PAR	**May 21, 2013**

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Fluarix
INN (or common name) of the active substance(s):	• A/California/7/2009 (H1N1) derived strain used NYMC X-181 • A/Perth/16/2009 (H3N2)-like strain used NYMC X-187 derived from A/Victoria/210/2009 • B/Brisbane/60/2008
MAH:	GlaxoSmithKline GmbH & Co. KG
Currently approved Indication(s):	Prophylaxis of influenza, especially in those who run an increased risk of associated complications. The use of Fluarix should be based on official recommendations.
Pharmaco-therapeutic group (ATC Code):	J07B B02
Pharmaceutical form(s) and strength(s):	Suspension for injection

LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
AE	Adverse event
ANCOVA	Analysis of Covariance
ATP	According-to-protocol
CBER	Center for Biologics Evaluation and Research
CI	Confidence Interval
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
DIL	Dilution
D-QIV	GSK Biologicals'candidate quadrivalent influenza vaccine (manufactured in Dresden)
EMA	European Medicine Agency
FDA	Food and Drug Administration
GMT	Geometric Mean Titre
GSK	GlaxoSmithKline
HA	Haemagglutinin
HI	Haemagglutination Inhibition
ILI	Influenza Like Illness
LD	Low Dose
LL	Lower limit
IM	Intramuscular
LAR	Legally Acceptable Representative
m	module
MAV	AE with Medically Attended Visit
MDCK	Madin-Darby Canine Kidney
MGI	Mean Geometric Increase
MN	Microneutralization
NH	Northern hemisphere
PCR	Polymerase chain reaction
pIMD	potential immune mediated disease
RBC	Red blood cell
RT-PCR	Reverse transcriptase-polymerase chain reaction
SAE	Serious adverse event
SCF	Seroconversion factor
SCR	Seroconversion Rate
SD	Standard deviation
SOP	Standard Operating Procedure
SPR	Seroprotection Rate
S-	Seronegative
S+	Seropositive
TF	Thimerosal-free
TIV	Trivalent inactivated Influenza Vaccine
TIV-1 (Fluarix)	*Fluarix* Trivalent Influenza Vaccine
TIV-2 Trivalent	*Fluarix* formulation containing the alternative lineage B strain (as contained in D-QIV) instead of the WHO/CBER recommended strain
VE	Vaccine Efficacy
US(A)	United States (of America)
UL	Upper limit
WHO	World Health Organization

I. EXECUTIVE SUMMARY

GlaxoSmithKline Biologicals submitted, for its Fluarix influenza seasonal vaccine (MRP, RMS is Germany, license n° PEI/H/00085/01/1), four (4) Articles 46 paediatric studies in which Fluarix is involved:

- FLU D-QIV-002
- FLU D-QIV-003
- FLU D-QIV-AS03-005
- FLU Q-QIV-003 PRI

Study FLU D-QIV-002 and-003 have been submitted during the approval procedure of Fluarix tetra. Hence, for more details on the QIV vaccine see Assessment Report DE/H/1939/001/DC. Here the focus will be on Fluarix.

II. RECOMMENDATION[1]

Based on the review of the paediatric data on safety and immunogenicity collected in the above mentioned studies the Rapporteur considers that the benefit-risk balance for Fluarix remains unchanged, however, the SmPC and PIL should be completed by the safety data obtained in children. As it is known from many other vaccines, in vaccinated children the reactogenicity is higher than in adult or elderly. This should be reflected in the SmPC.

The MAH should provide a proposal for wording of section 4.8 of the SmPC and section 4 of the PIL as mentioned in Section V (Rapporteur's Overall Conclusion and Recommendation). See also Section VI (Request for Supplementary Information).

On the 4th of April 2013 the MAH submitted a sufficient wording for the SmPC and the PIL. The issue is solved.

III. INTRODUCTION

On September 24, 2012 the MAH submitted four completed paediatric studies for Fluarix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

Fluarix was first approved on 4 July 1991 in Germany. To date, Fluarix has been registered in 106 countries.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Fluarix and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the studies

[1] *The recommendation from section V can be copied in this section*

GlaxoSmithKline Biologicals has been marketing an inactivated influenza split vaccine (Fluarix) since 1991. More than 200 million doses have been distributed worldwide and the vaccine is registered in more than 100 countries.
In 2005, Fluarix was approved under the accelerated approval regulation for adults. Noninferiority (NI) versus Fluzone was shown in adult and elderly populations, as well as clinical vaccine efficacy against culture confirmed influenza cases in a population 18 to 64 years of age. GSK is now pursuing a development in children. A clinical study was initiated in US in 2006/2007 with the Thimerosal-reduced registered product, Fluarix, and results have just been made available. Fluarix was shown to be safe and immunogenic in a population aged 6 months to 18 years of age. Although NI with respect to one or more immunogenicity parameters was demonstrated against Fluzone in children aged 3 years and above, the study failed to demonstrate NI in children below 3 years.
Of note, a Thimerosal-free formulation will be used for Fluarix in the 2008/2009 season. It has been proven more immunogenic than the Thimerosal-reduced formulation in children below 3 years of age (Fluarix 056 study) and was able to meet CHMP serological criteria set for adults aged 18 to 60 years. HI antibody titers have been shown to predict protection from infection as well as to correlate with vaccine effectiveness. Thus, the immunological non-inferiority demonstration against a pediatric licensed vaccine with proven efficacy against culture-confirmed influenza among children in one of two years studied is considered pivotal for establishing clinical benefit.

Fluarix-VB (Victoria lineage B strain) and *Fluarix*-YB (Yamagata lineage B strain) are GSK Biologicals' licensed trivalent vaccines formulated with the same two influenza A strains (A/H1N1 and A/H3N2), but with different B strains. *Fluarix*-VB was identical to *Fluarix* and *Fluarix*-YB contained an alternate Yamagata lineage B strain, but otherwise was also identical to *Fluarix*. The Victoria lineage B strain in *Fluarix*-VB was the B strain recommended by the WHO for the Northern Hemisphere 2010-2011 influenza season, while the Yamagata lineage B strain in *Fluarix*-YB was not included in the 2010-2011 season recommendation.
The quadrivalent FLU Q-QIV vaccine was formulated with two influenza A strains (A/H1N1 and A/H3N2) and two influenza B strains (the same Victoria lineage B strain as that in *Fluarix*-VB, as well as a second, Yamagata lineage, B strain). All vaccine formulations proposed to be used in this study were free of thimerosal.

Vaccine composition /dose:
Vaccine administered IM in the right deltoid at study entry (Day 0) and a second dose at Day 28 for unprimed subjects only:

FLU-D-QIV-002
Commercial *Fluarix* for the season 2009/2010 containing 15µg HA from three influenza strains (45 µg HA in total): A/Brisbane/59/2007 (H1N1 strain); A/Uruguay/716/07 (H3N2 strain) and B/Brisbane/60/2008 (Victoria-lineage) strain (*Lot number*: AFLUA445A)
FLU D-QIV: Haemagglutinin (HA) from four influenza strains (15 µg HA of each - 60µg HA in total): A/Brisbane/59/2007 (H1N1 strain); A/Uruguay/716/07 (H3N2 strain); B/Brisbane/60/2008 (Victoria-lineage) strain and B/Brisbane/3/2007 (Yamagata-lineage) strain.
(Lot number : DFLBA002A)

FLU-D-QIV-003
Commercial TIV-1 (*Fluarix)* (0.5 mL) for the season 2010/2011 containing
15µg HA from three influenza strains (45 µg HA in total): A/California/7/2009 (H1N1) strain;
A/Victoria/210/2009 (H3N2) strain and B/Brisbane/60/2008 (Victoria-lineage) strain. Dose administered was 0.5 mL. *Lot number:* AFLUVA521A
FLU-D-QIV: Haemagglutinin (HA) from four influenza strains (15 µg HA of each - 60µg

HA in total): A/California/7/2009 (H1N1) strain; A/Victoria/210/2009 (H3N2) strain; B/Brisbane/60/2008 (Victoria-lineage) strain and B/Brisbane/3/2007 (Yamagata-lineage) strain. Dose administered was 0.5 mL. *Lot number:* DFLBA0087A

FLU D-QIV-AS03-005

FLU D-QIV-AS03 vaccines The FLU D-QIV-AS03 vaccine was a quadrivalent split virion, inactivated influenza vaccine consisting of four monovalent viral antigen bulks. One dose of FLU D-QIV-AS03 vaccine contained 2.5 µg or 5.0 µg or 7.5 µg HA of each influenza virus strain. All study vaccines were adjuvanted with AS03 adjuvant that consisted of a tocopherol-based o/w emulsion. AS03D and AS03E contained 1.48 mg and 0.74 mg of tocopherol, respectively. Three of the four inactivated split virion antigens (monovalent bulks) used for the formulation of the quadrivalent influenza vaccine FLU D-QIV-AS03 were exactly the same as the active ingredients used for the formulation of GSK Biological's commercial trivalent split virion inactivated influenza vaccine Fluarix. These three strains (A/California/7/2009 (H1N1), A/Victoria/210/2009 X-187 (H3N2), B/Brisbane/60/2008) were the strains that were recommended by WHO for the Northern Hemisphere for 2010/11 season. In the quadrivalent FLU D-QIV-AS03 vaccine, an additional B strain from alternative lineage (B/Brisbane/3/2007) was added to the composition. All strains were derived from egg-grown viruses.

The FLU D-QIV-AS03 vaccine contained the following excipients: Polysorbate 80 (Tween 80), Octoxynol 10 (Triton X-100), alpha-tocopheryl hydrogen succinate, sodium chloride, magnesium chloride, disodium hydrogen phosphate, potassium dihydrogen phosphate, potassium chloride, alpha-tocopherol, squalene and water for injection.

QIV vaccine The QIV vaccine was a quadrivalent split virion, inactivated influenza vaccine consisting of four monovalent viral antigen bulks prepared respectively from influenza strains A/California/7/2009 (H1N1), A/Victoria/210/2009 X-187 (H3N2), B/Brisbane/60/2008 and a second B strain from alternative lineage (B/Brisbane/3/2007). One dose of QIV vaccine contained 15 µg HA of each influenza virus strain. QIV contained the following excipients: sodium chloride, disodium hydrogen phosphate, potassium dihydrogen phosphate, potassium chloride, magnesium chloride, alphatocopheryl hydrogen succinate, polysorbate 80 (Tween 80), octoxynol 10 (Triton X-100), and water for injection.

Fluarix

Fluarix contained 15 □g HA from three influenza strains recommended by WHO for the Northern Hemisphere (A/California/7/2009 (H1N1), A/Victoria/210/2009 X-187 (H3N2) and B/Brisbane/60/2008; total HA = 45 µg). Fluarix contained the following excipients: sodium chloride, disodium hydrogen phosphate, potassium dihydrogen phosphate, potassium chloride, magnesium chloride, alpha-tocopheryl hydrogen succinate, polysorbate 80 (Tween 80), octoxynol 10 (Triton X-100), and water for injection.

FLU Q-QIV-003 PRI

QIV: HA from 3 influenza strains (total HA/0.5 mL dose = 45 µg, 15 µg each): A/California/7/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria-lineage). Lot number: AFLUA521A (expiry date: 31-May-2011).

Fluarix-VB (TIV-VB) vaccine:

HA from 3 influenza strains (total HA/0.5 mL dose = 45µg, 15 µg each): A/California/7/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria-lineage). Lot number: AFLUA521A (expiry date: 31-May-2011).

Fluarix-YB (TIV-YB) vaccine:

HA from 3 influenza strains (total HA/0.5 mL dose = 45 µg, 15 µg each strain): A/California/7/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/3/2007 (Yamagata lineage).Lot number: DFLUA039A (expiry date: 30-Jun-2011).

The United States Food and Drug Administration (US FDA) and the European Medicine Agency (EMA) have issued recommendations as to the values that immunogenicity parameters characterizing influenza vaccines should reach for licensure (CBER, 2007; CPMP, 1997). These are described in Table 1.

Table 1: Acceptability criteria for HI antibody response set by CBER and CHMP

	CBER		CHMP	
	< 65 years	≥ 65 years	18-60 years	> 60 years
Seroconversion rate	LL of 95% CI ≥ 40%	LL of 95% CI ≥ 30%	> 40%	> 30%
Seroprotection rate	LL of 95% CI ≥ 70%	LL of 95% CI ≥ 60%	> 70%	> 60%
Mean Geometric Increase (Seroconversion factor)	No standard defined		> 2.5	> 2.0

CBER = Center for Biologics Evaluation and Research; CHMP = Committee for Medicinal Products for Human Use; CI= Confidence Interval; LL = Lower limit

Rapporteur's comment:
No CHMP criteria are defined for the evaluation of influenza vaccines in the paediatric population. However, in addition to the CBER criteria, which apply to the paediatric population, CHMP criteria for adults 18-60 years of age have also been considered when evaluating HI antibody responses in paediatric studies.

Hence, methodologies applied to investigate serological responses following vaccination are in line with current guidance on the clinical evaluation of influenza vaccines.

IV.2 Clinical aspects

1. Introduction

The MAH submitted final study reports for four different studies:

- FLU D-QIV-002 (18-47 months)
- FLU D-QIV-003 (6 months -17 years)
- FLU D-QIV-AS03-005
- FLU Q-QIV-003 PRI (included three parallel arms in children 3-17 years and one open-label independent arm in children 6-35 months

2. Clinical studies

FLU D-QIV-002 (EUdraCT 2012-002587-27)

➢ Description

Title of the study: A phase II, double-blind, multicentre, randomized study to evaluate the immunogenicity and safety of GSK Biologicals' quadrivalent influenza candidate vaccine GSK2321138A compared with GSK Biologicals' trivalent influenza vaccine, *Fluarix*, administered intramuscularly in children (18-47 months of age) in both unprimed subjects and in primed subjects who previously participated in the 111751 study (Fluarix-US-007).

➢ Methods

- Objective(s)

The primary objective was to assess the immunological non-inferiority in terms GMTs of the D-QIV vaccine compared to *Fluarix* in primed and unprimed subjects for the three recommended seasonal strains, 28 days after the last vaccination. Secondary objectives included the evaluation of the immunological superiority in terms of GMTs of D-QIV vaccine compared to *Fluarix* for the B strain that is not included in the trivalent influenza vaccine, 28 days after the last vaccination. Also, the immunological superiority of the HI responses to each of the B strains contained in D-QIV in primed versus unprimed children after one vaccine dose was evaluated (i.e. both homologous and heterologous primings). Descriptive immunogenicity and safety/ reactogenicity were assessed as well.

- Study design

Multi-centre, double-blinded controlled study in four parallel groups with 600 subjects aged 18-47 months performed in Mexico.
Treatment groups:

- Group primed TIV : 100 primed subjects receiving 1 dose of *Fluarix*
- Group unprimed TIV: 200 unprimed subjects receiving 2 doses of *Fluarix*
- Group primed QIV: 100 primed subjects receiving 1 dose of FLU D-QIV
- Group unprimed QIV: 200 unprimed subjects receiving 2 doses of FLU D-QIV

For primed subjects:

- o One intramuscular (IM) injection at Day 0. A blood sample was collected on Day 0 and 28

For unprimed subjects:

- o Two IM injections at Day 0 and 28. A blood sample was collected on Day 0 and 28 or 56.

For all subjects:

- o A phone contact/visit was scheduled at Day 180 to record AEs.

Duration of study was approximately 6 months for each subject.

- Study population /Sample size

Healthy children, 18-47 months of age, either previously vaccinated with 2 doses of *Fluarix* in study Fluarix-US-007, or not having been vaccinated with a 2-dose schedule for influenza in any previous season.

Planned: 600 subjects (TIV: 300 subjects, QIV: 300 subjects)

- Treatments

Fluarix vaccine administered IM in the right deltoid at study entry (Day 0) and a second dose at Day 28 for unprimed subjects only.

- Outcomes/endpoints

Primary endpoint:
Humoral immune response in terms of Haemagglutination Inhibition (HI) antibodies.

Observed variables

- At pre-vaccination (Day 0) and 28 days post last vaccination (Day 28 or Day 56) time points: serum anti-HI antibody titer against the three vaccine strains contained in *Fluarix*.

Derived variables
The following parameters (with 95% confidence intervals (CIs)) were to be calculated for each treatment group and each strain:

- GMT at the post-vaccination time points (Day 28 or Day 56), 28 days after the last vaccination.

Secondary endpoint:
Humoral immune response in terms of HI antibodies.
Observed variables

- At pre-vaccination (Day 0) and 28 days post first vaccination (Day 28) and post second vaccination (Day 56) time points: serum anti-HI antibody titer against all 4 vaccine strains.

Derived variables
The following parameters (with 95% CIs) were to be calculated for each treatment group and for all vaccine strains:

- GMT of HI antibody titers at Days 28 and 56.
- Seropositivity rates at Days 0, 28 and 56.
- Seroconversion rates (SCR)* at Days 28 and 56.
- Seroconversion factors (SCF)** at Days 28 and 56.
- Seroprotection rates (SPR)*** at Days 0, 28 and 56. * SCR is defined as the percentage of vaccinees who have either a pre-vaccination titer <1:10 and a postvaccination titer ≥1:40 or a pre-vaccination titer ≥1:10 and at least a four-fold increase in postvaccination titer.

**SCF is defined as the fold increase in serum HI GMTs post-vaccination compared to Day 0.
***SPR is defined as the percentage of vaccinees with a serum HI titer ≥1:40 that usually is accepted as indicating protection in at least 50% of vaccinees [Hobson, 1972].

Safety /reactogenicity:

- Solicited local and general symptoms
- Occurrence, intensity and duration of solicited local AEs during a 7-day follow-up period (i.e. day of vaccination and 6 subsequent days) after each vaccination.
- Occurrence, intensity, duration and relationship to vaccination of solicited general AEs during a 7-day follow-up period (i.e. day of vaccination and 6 subsequent days) after each vaccination.
- Unsolicited AEs
- Occurrence, intensity and relationship to vaccination of unsolicited AEs during a 28-day follow-up period (i.e. day of vaccination and 27 subsequent days) after each vaccination.
- SAEs
- Occurrence and relationship to vaccination of SAEs during the entire study period.
- AESI
- Occurrence and relationship to vaccination of AESI during the entire study period.

- Statistical Methods

Rapporteur's comment:
Statistical tools chosen to investigate immunogenicity and safety were appropriate.

➢ **Results D-QIV-002**

- Recruitment/ Number analysed

Enrolled:	599 subjects (TIV: 301 subjects and QIV: 298 subjects)
Completed:	584 subjects (TIV: 293 subjects and QIV: 291 subjects)
Safety:	Total vaccinated cohort: 599 subjects (TIV: 301 subjects and QIV: 298 subjects)
Immunogenicity:	585 subjects in the According To Protocol (ATP) cohort for immunogenicity (TIV: 295 subjects and QIV: 290 subjects)

Rapporteur's comment:
No undue loss of participants was observed. Numbers analysed in the ATP cohorts are sufficiently high. The true target groups included in EU recommendations for seasonal influenza vaccine, i.e. individuals with acute or chronic underlying disease had not been included in the study.

- Baseline data

The mean age was 31.4 and 31.6 months in the QIV and TIV groups, respectively. In total, 47.6% of subjects were female and 100% of the population was of American Hispanic or Latino ethnicity.

Pre-vaccination seropositivity rates were of 48.7% and 45.3% for A/H1N1, 52.1% and 52.6% for A/H3N2, 21.6% and 24.5% for B/Victoria, and 49.2% and 57.8% for the B/Yamagata in the D-QIV and *Fluarix* groups, respectively. Pre-vaccination titers ranged from 18.6 to 22.2 for both A strains. Baseline titers against the two B strains were of 8.7 and 9.0 against B/Victoria, and of 15.8 and 20.6 against B/Yamagata. These baseline seropositivity rates and baseline titers are lower than those in subjects 3-17 years of age in study D-QIV-003 (see below).

In study D-QIV-002, 35%-45% of subjects had pre-vaccination antibody levels <1/40 for A/H1N1, A/H3N2 and B/Yamagata. Lower pre-vaccination SPR was observed against B/Victoria in both D-QIV and *Fluarix* groups (16.3% - 18.2%).
High pre-vaccination seropositivity levels for neutralizing antibodies were observed, being highest for A/H3N2 (85.9% and 92.6% with GMT 86.0 and 108.3), followed by A/H1N1 (75.0% and 76.8% with GMT 78.2 and 87.0) and B strains B/Yamagata and B/Victoria (range 50.5% to 60.0% with lower GMT range, i.e. 33.5 to 41.3).

- Efficacy results

The immunological non-inferiority in terms of GMTs of the FLU D-QIV vaccine compared to *Fluarix* was demonstrated for the three recommended seasonal strains 28 days after the last vaccination.
The immunological superiority in terms of GMTs of the FLU D-QIV vaccine compared to *Fluarix* in primed and unprimed subjects for the B strain that is not included in the TIV vaccine 28 days after the last vaccination was demonstrated.

Table 2: HI Antibodies measured on Day 0 and 28 days after last vaccination against the four strains (ATP cohort for immunogenicity)

			>= 10 1/DIL			GMT			SCR			SPR			SCF		
				95% CI			95% CI			95% CI			95% CI			95% CI	
Grou	Timin	N	%	LL	UL	valu	LL	UL	%	LL	UL	%	LL	UL	valu	LL	UL
FLU A/Bri/59/07 H1N1.HA Ab																	
QIV	PRE	18	48.	41.	56.	22.2	17.2	28.7	-	-	-	38.	31.	46.	-	-	-
	POST	19	94.	90.	97.	173.	141.	213.	58.	51.	65.	87.	81.	91.	7.6	6.2	9.5
TIV	PRE	19	45.	38.	52.	21.6	16.7	28.0	-	-	-	38.	31.	45.	-	-	-
	POST	19	94.	90.	97.	176.	143.	218.	66.	59.	73.	89.	83.	93.	8.2	6.7	10.0
Flu A/Uru/716/07 H3N2.HA Ab																	
QIV	PRE	19	52.	44.	59.	18.6	14.9	23.2	-	-	-	37.	30.	44.	-	-	-
	POST	19	96.	93.	98.	120.	101.	143.	66.	59.	73.	88.	83.	92.	6.5	5.5	7.6
TIV	PRE	19	52.	45.	59.	20.8	16.5	26.2	-	-	-	37.	30.	44.	-	-	-
	POST	19	95.	92.	98.	130.	108.	157.	63.	55.	69.	90.	85.	94.	6.3	5.3	7.4
FluB/Bri/60/08 Victoria.HA Ab																	
QIV	PRE	19	21.	16.	28.	8.7	7.3	10.2	-	-	-	16.	11.	22.	-	-	-
	POST	19	82.	76.	87.	61.9	48.7	78.6	65.	57.	71.	69.	62.	76.	7.0	5.9	8.4
TIV	PRE	19	24.	18.	31.	9.0	7.7	10.6	-	-	-	18.	13.	24.	-	-	-
	POST	19	82.	76.	87.	66.6	52.4	84.7	66.	59.	72.	72.	65.	78.	7.4	6.1	8.9
Flu B/Bri/3/07 Yamagata.HA Ab																	
QIV	PRE	18	49.	41.	56.	15.8	13.1	19.0	-	-	-	38.	31.	45.	-	-	-
	POST	19	99.	96.	99.	276.	239.	318.	91.	86.	94.	97.	94.	99.	17.1	14.	20.6
TIV	PRE	19	57.	50.	64.	20.6	16.9	25.1	-	-	-	44.	37.	52.	-	-	-
	POST	19	85.	79.	89.	72.6	59.5	88.7	42.	35.	50.	77.	70.	82.	3.5	3.0	4.1

QIV = Subjects received 1 or 2 doses of Flu D-QIV TIV = Subjects received 1 or 2 doses of Fluarix
N = number of subjects with available results 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Pre-vaccination at Day 0 POST = Post-vaccination 28 days after the last vaccination
GMT = geometric mean antibody titre calculated on all subjects Seroconversion defined as:
For initially seronegative subjects, antibody titre >= 40 1/DIL after vaccination For initially seropositive subjects, antibody titre after vaccination >= 4 fold the pre-vaccination antibody titre SCF = Fold increase in serum HI GMTs post-vaccination SPR = percentage of vaccinees with serum H1N1 HI antibody titer≥ 1:40

A total of 301 subjects received one or two doses of Fluarix. The administration of Fluarix to children 18-47 months elicited a humoral immune response in terms of HI against the 3 strains contained in Fluarix, as evaluated 28 days after the last vaccination. The CHMP criteria and the CBER criteria for post-vaccination SCR were met for all three strains included in Fluarix. For post vaccination SPR, criteria were also met for all three strains except for B/Victoria strain (QIV)

for which CBER criterion was not met. The MGI CHMP criterion was met for all three strains post vaccination.

- Safety results (D-QIV-002)

The safety analysis was performed on the TVC. In subjects aged 18 to 47 months site pain was the most frequently reported local AE (reported in 42.7% of the subjects in the D-QIV group and in 38.9% in the TIV group). Pain incidences following the first and the second dose were 36.2% and 32.1% for the D-QIV vaccine, and 34.2% and 28.3% for TIV vaccine. Redness and swelling were less common than pain and were reported at similar rates in both treatment groups. There was no evidence of increased local reactogenicity following administration of the second dose compared to the first dose. In the Fluarix group, irritability (29.2%) and loss of appetite (28.9%) were the most frequently reported general AEs. Grade 3 solicited general AEs, including fever, were reported with a very low incidence rate (below 0.7% of doses). 39.2% (4% Grade 3) of the subjects from the Fluarix group experienced at least one unsolicited AE. Most frequently reported was nasopharingitis. The incidences of MAEs (Medically attended events) were similar in both vaccine groups. In this age group one-third saw a doctor within 28 days after the administration of the vaccine. This rate is twofold higher in this age group than in children aged 3-17 years. However, this is not remarkable as younger children do have more infections compared to older kids or adolescents. As in study QIV-003, also in in this study nasopharyngitis was the most frequently reported MAE in both groups (20.1 % in the QIV group vs. 20.9% in the Fluarix group). No AEs of specific interest were reported within the 180-day post-vaccination follow-up period. Two subjects from the Fluarix group experienced at least one SAE. Those two events resolved. No SAE assessed as causally related to Fluarix vaccination were reported. One subject suffered from febrile convolution. It was not considered related to the vaccine.
No subject was withdrawn due to an AE. No fatal SAE was reported during the 180-day safety follow-up.

3. Discussion on clinical aspects D-QIV-002

While relatively high baseline immunity rates are expected for older children, adolescents, adults and the elderly in terms of seropositivity rates, seroprotection rates and GMTs, such observations are rather unexpected and unusual for younger children, in particular those from 6 – 35 months of age. Pre-vaccination seropositivity levels as measured by the HI assay ranging from 48.7% and 45.3% for A/H1N1, 52.1% and 52.6% for A/H3N2, 21.6% and 24.5% for B/Victoria, and 49.2% and 57.8% for the B/Yamagata in the D-QIV and *Fluarix* groups, respectively, are unrealistically high since it is unlikely that very young children have been exposed to all three circulating influenza virus strains in such dimensions and previous vaccination was defined as an exclusion criterion.
Moreover, seropositivity ranges as measured by the MN assay were even higher in these young age groups. These findings suggest that both, HI and VN assays are rather unspecific indicating that antibodies which are not influenza antigen specific contribute to these extremely high test readouts. This is a major issue questioning the validity of the overall serological findings.

Rapporteur´s comment:
Fluarix, administered in children 18-47 months of age in study D-QIV-002 (N=301), was shown to be generally well-tolerated. However, the safety data obtained in this study are not in line with point 4.8 of the current Fluarix SmPC/PL (e.g. 18-47 months: pain, loss of appetite or irritability is very common) and therefore an adoption of the SmPC seems to be necessary.

FLU D-QIV-003 (EUdra-2010-021032-34)

- **Description**

A phase III, randomized, double-blind, controlled, multi-country, multi-centre study to evaluate the immunogenicity and safety of GSK Biologicals' quadrivalent influenza vaccine compared to GSK Biologicals' trivalent influenza vaccine administered IM in children 3 to 17 years old and to describe the safety and immunogenicity of GSK Biologicals'quadrivalent influenza vaccine in children 6 to 35 months old.
Study centres: Multi-centre study conducted in 55 centres across Czech Republic, France, Germany, Philippines and the USA.

- **Methods**

- Objectives

Primary objective:
- To evaluate the immunological non-inferiority (in terms of Geometric Mean Titre (GMT) and Seroconversion Rate (SCR)) of D-QIV versus TIV-1 (*Fluarix*) and TIV- 2 in children (3 to 17 years) at 28 days (primed subjects) or 56 days (unprimed subjects) following first vaccination (28 days after completion of the immunization series)

Secondary objectives:
- To evaluate the immunological superiority (in terms of GMTs and SCR) of D-QIV versus TIV-1 (*Fluarix*) and TIV-2 in children (3 to 17 years) at 28 days (primed subjects) or 56 days (unprimed subjects) following first vaccination (28 days after completion of the immunization series) for the B strain not contained in each TIV formulation.
- To describe the immunogenicity (in terms of GMT, seroprotection rate (SPR), SCR and mean geometric increase (MGI)) of D-QIV, TIV-1(*Fluarix*) and TIV-2 for all subjects, and of D-QIV for the 6 to 35 month age group.
- To evaluate the safety and reactogenicity of D-QIV, TIV-1 (*Fluarix*) and TIV-2 in the 3 to 17 years age category and to evaluate the safety and reactogenicity of D-QIV for the 6 to 35 month age group, with regard to:
- Solicited local adverse events (AEs) during the 7-day post-vaccination follow-up (day of vaccination and 6 subsequent days).
- Solicited general AEs during the 7-day post-vaccination follow-up (day of vaccination and 6 subsequent days).
- Unsolicited AEs during the 28-day (day of vaccination and 27 subsequent days) post-vaccination follow-up period.
- SAEs, pIMDs, and MAV during the entire study period.

- Study design

The design of study D-QIV-003 was based, for vaccination schedule, on the current *Fluarix* indication and in line with recommendations of the Advisory Committee on Immunization Practices (ACIP), i.e. the administration of one dose to all children, except unprimed children below the age of 9 to whom a second dose should be administered, with an interval of 4 weeks between both doses. To further support the adequacy of this vaccination schedule, an analysis of the immune response was performed, according to the priming status in children 3 to 8 years old, and compared to children 9-17 years old.
Blood sampling was done as follows:

- For primed subjects < 9 years and all subjects aged from 9 to 17 years: a blood sample was collected at Days 0 and 28.
- For unprimed subjects < 9 years: a blood sample was collected at Days 0 and 56.

- Study population /Sample size/Treatments

Healthy subjects were enrolled and randomized (1:1:1) to one of the following study groups:
- D-QIV: 915 subjects 3-17 years old, receiving one or two doses of D-QIV vaccine (double blind)
- *Fluarix*: 914 subjects 3-17 years old, receiving one or two doses of *Fluarix* (doubleblind)
- TIV-2: 912 subjects 3-17 years old, receiving 1 or 2 doses of TIV-2 (alternative trivalent formulation, containing the additional B strain included in D-QIV as B strain, and otherwise identical to *Fluarix*) (double-blind)
- D-QIV-Y: 277 subjects 6-35 months old, receiving 1 or 2 doses of D-QIV vaccine (open arm)

The treatment was stratified by age strata with a ratio of 2:1 for children from 3-8 years and 9-17 years. Subjects were vaccinated either with one dose at Day 0 (primed subjects), or with 2 vaccine doses at Days 0 and 28 (unprimed subjects). Primed children were defined as subjects who are ≥9 years or who are < 9 years and have had at least one dose of an influenza A (H1N1) 2009 monovalent vaccine in the previous season (or had laboratory-confirmed H1N1 infection) and have received two doses of seasonal influenza immunizations separated by at least one month during the previous season or have received at least one dose prior to the previous season. Unprimed children were subjects who had not received any influenza A (H1N1) 2009 monovalent vaccine in the previous season (or did not have laboratory-confirmed H1N1 infection) or who had not received any seasonal influenza immunization in the past or received only one dose of influenza vaccine for the first time in the previous influenza season.

- Outcomes/endpoints

Primary endpoint
Humoral immune response in terms of HI antibodies.
Serum anti-HA antibody titres against the four vaccine strains at Day 0 and 28 days after last vaccine dose in each group were used to calculate:
- GMTs of HI antibody titres at Day 0 and 28 days after last vaccine dose in each group.
- SCR* 28 days after last vaccine dose.

Secondary endpoint
Immunology:
Humoral immune response in terms of HI antibodies.
☐Serum anti-HA antibody titres against the four vaccine strains at Day 0 and 28 days after last vaccine dose in each group stratified by age (6 to 35 months, 3 to 8 years and 9 to 17 years) were used to calculate:
- GMTs of HI antibody titres at Day 0 and 28 days after last vaccine dose.
- SCR* for the three strains 28 days after last vaccination.
- SPR** at Day 0 and 28 days after last vaccine dose.
- MGI*** 28 days after last vaccine dose.

Safety:
Solicited local AEs
- Occurrence, duration and intensity during a 7-day follow-up period (i.e. day of vaccination and 6 subsequent days) after each vaccination in each group.

Solicited general AEs
- Occurrence, duration, intensity and relationship to vaccination during a 7-day follow-up

period (i.e. day of vaccination and 6 subsequent days) after each vaccination, in each group.

Unsolicited AEs

- Occurrence, intensity and relationship to vaccination during a 28-day follow-up period (i.e. day of vaccination and 27 subsequent days) after each vaccination, in each group.

SAEs and pIMDs

- Occurrence and relationship to vaccination during the entire study period in each group.
- AEs that led to a MAV
- Occurrence, intensity and relationship to vaccination during the entire study period in each group.

- Statistical Methods

Rapporteur's comment:
Statistical tools chosen to investigate immunogenicity and safety were appropriate.

➢ **Results D-QIV-003**

- Recruitment/ Number analysed

Rapporteur's comment:
No undue loss of participants was observed. Individuals with acute and/or chronic underlying disease belonging to the key target groups for seasonal influenza vaccination had not been included.

- Baseline data

In study D-QIV-003, subjects 3-17 years old had pre-vaccination seropositivity levels ranging from 63.5% to 68.9% for A/H1N1, from 79.1% to 82.2% for A/H3N2, from 78.0% to 78.5% for B/Victoria and from 92.1% to 92.9% for B/Yamagata. As expected, the pre-vaccination seropositivity levels of the younger group with subjects 6- 35 months of age (D-QIV-Y group) were lower, i.e. 31.0% (A/H1N1), 22.0% (A/H3N2), 30.6% (B/Victoria) and 53.4% (B/Yamagata). Before vaccination, comparable GMT levels were observed across groups in the 3-17 year age range: GMTs against A/H1N1 were 21.6, 24.9, and 22.1 in the D-QIV, *Fluarix* and TIV-2 groups, respectively. HI antibody GMTs against A/H3N2 were of 29.0, 31.4 and 31.2 in those same groups. Values between 30.9 and 33.2 were obtained against B/Victoria, and between 77.2 and 84.7 for the B/Yamagata strain. In line with the lower seropositivity rates, pre-vaccination GMTs observed in the D-QIV-Y group were 12.3, 8.6, 9.0 and 13.1 against A/H1N1, A/H3N2, B/Victoria and B/Yamagata, respectively. Approximately half of the subjects 3-17 years old had prevaccination titres <1/40 for A/H1N1, A/H3N2 and B/Victoria strains. Seroprotection rates ranged from 43.4% to 49.3% (A/H1N1), from 48.2% to 51.1% (A/H3N2) and from 48.2% to 49.9% (B/Victoria). Higher pre-vaccination SPR were already found for the B/Yamagata strain, i.e. from 70.2% to 74.1%, therefore meeting CHMP criterion (as defined for adults 18-60 years of age) and LL of 95% CI were close to the CBER criterion for this parameter. In subjects 6-35 months old, lower pre-vaccination SPR were observed, i.e. 25.9%, 14.7%, 12.1% and 20.7% for A/H1N1, A/H3N2, B/Victoria and B/Yamagata, respectively.

Immunogenicity results D-QIV-003

The administration of Fluarix to children 3-17 years elicited a humoral immune response in terms of HI as evaluated at 28 days after the last vaccination that exceeded CHMP criteria (for adults 18-60 years) and CBER criteria (for the pediatric population) for all three strains included in Fluarix.

Table 3: Study D-QIV-003: Seropositivity rates and GMTs for HI antibody titers at day 0 and day 28 or day 56 - by priming status and age category (ATP cohort for immunogenicity)

					≥ 1:10				GMT		
							95% CI			95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL
A/California/7/2009 (H1N1)	D-QIV	3-8 unprimed	PRE	410	233	**56.8**	51.9	61.7	**18.6**	16.3	21.2
			POST	411	410	**99.8**	98.7	100	**343.8**	309.1	382.3
		3-8 primed	PRE	78	63	**80.8**	70.3	88.8	**36.4**	27.0	49.2
			POST	78	78	**100**	95.4	100	**408.5**	310.2	537.9
		9-17 primed	PRE	302	215	**71.2**	65.7	76.2	**23.2**	20.2	26.6
			POST	302	302	**100**	98.8	100	**445.8**	393.9	504.7
	FLUARIX	3-8 unprimed	PRE	429	265	**61.8**	57.0	66.4	**21.9**	19.3	24.9
			POST	428	424	**99.1**	97.6	99.7	**391.8**	351.9	436.3
		3-8 primed	PRE	82	65	**79.3**	68.9	87.4	**23.7**	18.4	30.4
			POST	82	81	**98.8**	93.4	100	**335.2**	251.6	446.6
		9-17 primed	PRE	308	234	**76.0**	70.8	80.6	**30.2**	26.1	34.9
			POST	308	308	**100**	98.8	100	**533.3**	474.9	599.0
	TIV-2	3-8 unprimed	PRE	422	244	**57.8**	52.9	62.6	**20.7**	18.1	23.8
			POST	423	421	**99.5**	98.3	99.9	**373.9**	334.9	417.4
		3-8 primed	PRE	81	67	**82.7**	72.7	90.2	**33.5**	25.7	43.8
			POST	81	80	**98.8**	93.3	100	**422.7**	332.1	537.9
		9-17 primed	PRE	297	197	**66.3**	60.6	71.7	**21.5**	18.6	24.8
			POST	297	297	**100**	98.8	100	**502.0**	444.1	567.5
	D-QIV-Y	overall	PRE	232	72	**31.0**	25.1	37.4	**12.3**	10.2	14.8
			POST	234	227	**97.0**	93.9	98.8	**140.0**	113.7	172.3
A/Victoria/210/2009 (H3N2)	D-QIV	3-8 unprimed	PRE	410	302	**73.7**	69.1	77.9	**28.2**	24.8	32.0
			POST	411	411	**100**	99.1	100	**257.7**	236.8	280.4
		3-8 primed	PRE	78	61	**78.2**	67.4	86.8	**36.2**	26.7	49.2
			POST	78	78	**100**	95.4	100	**190.3**	149.7	241.8
		9-17 primed	PRE	302	266	**88.1**	83.9	91.5	**28.5**	25.1	32.3
			POST	302	301	**99.7**	98.2	100	**204.1**	185.5	224.5
	FLUARIX	3-8 unprimed	PRE	429	333	**77.6**	73.4	81.5	**32.8**	28.8	37.3
			POST	428	427	**99.8**	98.7	100	**261.4**	239.7	285.0
		3-8 primed	PRE	82	65	**79.3**	68.9	87.4	**33.6**	25.0	45.1
			POST	82	82	**100**	95.6	100	**162.1**	129.6	202.7
		9-17 primed	PRE	308	275	**89.3**	85.3	92.5	**29.0**	25.8	32.7
			POST	308	307	**99.7**	98.2	100	**204.9**	185.4	226.6
	TIV-2	3-8 unprimed	PRE	422	310	**73.5**	69.0	77.6	**31.7**	27.8	36.3
			POST	423	423	**100**	99.1	100	**262.4**	239.4	287.7
		3-8 primed	PRE	81	64	**79.0**	68.5	87.3	**30.4**	23.0	40.2
			POST	81	80	**98.8**	93.3	100	**168.4**	133.5	212.3
		9-17 primed	PRE	297	259	**87.2**	82.9	90.8	**30.8**	27.0	35.1
			POST	297	297	**100**	98.8	100	**217.5**	196.9	240.2
	D-QIV-Y	overall	PRE	232	51	**22.0**	16.8	27.9	**8.6**	7.4	9.9
			POST	234	232	**99.1**	96.9	99.9	**87.5**	73.8	103.7

					≥ 1:10				GMT		
							95% CI			95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL
B/Brisbane/60/2008 (Victoria)	D-QIV	3-8 unprimed	PRE	410	285	**69.5**	64.8	73.9	**24.7**	21.6	28.3
			POST	411	411	**100**	99.1	100	**240.6**	217.6	266.1
		3-8 primed	PRE	78	69	**88.5**	79.2	94.6	**43.5**	32.7	57.8
			POST	78	78	**100**	95.4	100	**214.6**	169.1	272.3
		9-17 primed	PRE	302	265	**87.7**	83.5	91.2	**38.3**	33.4	43.9
			POST	302	302	**100**	98.8	100	**257.5**	230.7	287.5
	FLUARIX	3-8 unprimed	PRE	429	284	**66.2**	61.5	70.7	**22.8**	20.0	26.0
			POST	428	426	**99.5**	98.3	99.9	**232.2**	209.7	257.1
		3-8 primed	PRE	82	75	**91.5**	83.2	96.5	**41.5**	32.0	53.9
			POST	82	82	**100**	95.6	100	**177.2**	143.8	218.3
		9-17 primed	PRE	308	280	**90.9**	87.1	93.9	**43.9**	38.2	50.6
			POST	308	308	**100**	98.8	100	**289.8**	262.1	320.4
	TIV-2	3-8 unprimed	PRE	422	289	**68.5**	63.8	72.9	**25.1**	21.9	28.8
			POST	423	409	**96.7**	94.5	98.2	**74.2**	65.8	83.7
		3-8 primed	PRE	81	73	**90.1**	81.5	95.6	**48.5**	37.1	63.4
			POST	81	81	**100**	95.5	100	**111.1**	89.7	137.7
		9-17 primed	PRE	297	266	**89.6**	85.5	92.8	**44.7**	38.6	51.7
			POST	297	294	**99.0**	97.1	99.8	**106.4**	94.6	119.8
	D-QIV-Y	overall	PRE	232	71	**30.6**	24.7	37.0	**9.0**	7.9	10.4
			POST	234	227	**97.0**	93.9	98.8	**86.4**	72.6	102.9
B/Brisbane/3/2007 (Yamagata)	D-QIV	3-8 unprimed	PRE	410	363	**88.5**	85.0	91.5	**50.0**	43.8	57.0
			POST	411	411	**100**	99.1	100	**477.3**	436.0	522.5
		3-8 primed	PRE	78	77	**98.7**	93.1	100	**89.7**	68.4	117.7
			POST	78	78	**100**	95.4	100	**503.4**	409.9	618.3
		9-17 primed	PRE	302	294	**97.4**	94.8	98.8	**134.3**	115.2	156.5
			POST	302	302	**100**	98.8	100	**748.1**	676.9	826.8
	FLUARIX	3-8 unprimed	PRE	429	367	**85.5**	81.9	88.7	**48.4**	42.2	55.5
			POST	428	427	**99.8**	98.7	100	**159.2**	142.8	177.4
		3-8 primed	PRE	82	81	**98.8**	93.4	100	**75.0**	58.4	96.3
			POST	82	82	**100**	95.6	100	**187.9**	152.0	232.3
		9-17 primed	PRE	308	306	**99.4**	97.7	99.9	**149.3**	130.3	171.1
			POST	308	308	**100**	98.8	100	**380.6**	342.1	423.4
	TIV-2	3-8 unprimed	PRE	422	370	**87.7**	84.2	90.7	**52.4**	45.8	59.8
			POST	423	423	**100**	99.1	100	**568.8**	520.7	621.3
		3-8 primed	PRE	81	78	**96.3**	89.6	99.2	**94.5**	70.2	127.1
			POST	81	81	**100**	95.5	100	**555.7**	455.3	678.4
		9-17 primed	PRE	297	290	**97.6**	95.2	99.0	**162.8**	140.4	188.6
			POST	297	297	**100**	98.8	100	**797.9**	719.5	885.0
	D-QIV-Y	overall	PRE	232	124	**53.4**	46.8	60.0	**13.1**	11.4	15.2
			POST	234	234	**100**	98.4	100	**167.7**	144.1	195.3

D-QIV = Subjects of 3-17 years received D-QIV *Fluarix* = Subjects of 3-17 years received *Fluarix* (contained the B Victoria strain) TIV-2 = Subjects of 3-17 years received TIV-2 (contained the B Yamagata strain) D-QIV-Y = Subjects of 6-35 months received D-QIV 3-8 unprimed = Unprimed subjects of 3-8 years of age; 3-8 primed = Primed subjects of 3-8 years of age 9-17 primed = Primed subjects of 9-17 years of age GMT = geometric mean antibody titre calculated on all subjects N = number of subjects with available results n/% = number/percentage of subjects with titre within the specified range 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit PRE = Pre-vaccination at Day 0 POST = Post-vaccination at 28 days after the last vaccination

Rapporteur's comment:
Seropositivity rates seem to be unexpectedly high pre-vaccination and post-vaccination, specifically in the youngest age group, i.e. in the open-label independent arm with D-QIV in children from 6 – 35 months of age. At least for those being seronegative (no HI titre measurable against on or more virus strains) one would have expected response rates differing from those being seropositive.

Table 4: Study D-QIV-003: Seroprotection rates (SPR HI titer ≥ 40), Seroconversion rate (SCR) and Mean Geometric Increase (MGI) for HI antibody titers at day 28 or 56 - by priming status and age category (ATP cohort for immunogenicity)

					SPR					SCR				MGI		
							95% CI					95% CI			95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL	N	n	%	LL	UL	Value	LL	UL
A/California/7/2009 (H1N1)	D-QIV	3-8 unprimed	PRE	410	163	**39.8**	35.0	44.7								
			POST	411	396	**96.4**	94.1	97.9	410	382	**93.2**	90.3	95.4	**18.7**	16.9	20.7
		3-8 primed	PRE	78	43	**55.1**	43.4	66.4								
			POST	78	73	**93.6**	85.7	97.9	78	65	**83.3**	73.2	90.8	**11.2**	8.3	15.2
		9-17 primed	PRE	302	137	**45.4**	39.7	51.2								
			POST	302	295	**97.7**	95.3	99.1	302	275	**91.1**	87.3	94.0	**19.2**	16.7	22.2
	FLUARIX	3-8 unprimed	PRE	429	199	**46.4**	41.6	51.2								
			POST	428	415	**97.0**	94.9	98.4	428	400	**93.5**	90.7	95.6	**17.8**	16.0	19.8
		3-8 primed	PRE	82	35	**42.7**	31.8	54.1								
			POST	82	76	**92.7**	84.8	97.3	82	68	**82.9**	73.0	90.3	**14.2**	10.8	18.5
		9-17 primed	PRE	308	170	**55.2**	49.5	60.8								
			POST	308	302	**98.1**	95.8	99.3	308	267	**86.7**	82.4	90.3	**17.7**	15.2	20.5
	TIV-2	3-8 unprimed	PRE	422	185	**43.8**	39.0	48.7								
			POST	423	407	**96.2**	93.9	97.8	422	387	**91.7**	88.7	94.2	**18.2**	16.4	20.2
		3-8 primed	PRE	81	45	**55.6**	44.1	66.6								
			POST	81	80	**98.8**	93.3	100	81	70	**86.4**	77.0	93.0	**12.6**	9.9	16.1
		9-17 primed	PRE	297	123	**41.4**	35.8	47.2								
			POST	297	291	**98.0**	95.7	99.3	297	276	**92.9**	89.4	95.6	**23.3**	20.3	26.9
	D-QIV-Y	overall	PRE	232	60	**25.9**	20.4	32.0								
			POST	234	187	**79.9**	74.2	84.9	232	181	**78.0**	72.1	83.2	**11.7**	10.2	13.4
A/Victoria/210/2009 (H3N2)	D-QIV	3-8 unprimed	PRE	410	210	**51.2**	46.3	56.2								
			POST	411	404	**98.3**	96.5	99.3	410	323	**78.8**	74.5	82.6	**9.1**	8.2	10.2
		3-8 primed	PRE	78	43	**55.1**	43.4	66.4								
			POST	78	73	**93.6**	85.7	97.9	78	44	**56.4**	44.7	67.6	**5.2**	3.9	7.0
		9-17 primed	PRE	302	128	**42.4**	36.7	48.2								
			POST	302	298	**98.7**	96.6	99.6	302	204	**67.5**	62.0	72.8	**7.2**	6.2	8.2
	FLUARIX	3-8 unprimed	PRE	429	234	**54.5**	49.7	59.3								
			POST	428	418	**97.7**	95.7	98.9	428	318	**74.3**	69.9	78.4	**7.9**	7.1	8.8

					SPR					SCR				MGI		
							95% CI					95% CI			95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL	N	n	%	LL	UL	Value	LL	UL
		3-8 primed	PRE	82	43	**52.4**	41.1	63.6								
			POST	82	78	**95.1**	88.0	98.7	82	47	**57.3**	45.9	68.2	**4.8**	3.8	6.2
		9-17 primed	PRE	308	135	**43.8**	38.2	49.6								
			POST	308	304	**98.7**	96.7	99.6	308	213	**69.2**	63.7	74.3	**7.1**	6.2	8.1
	TIV-2	3-8 unprimed	PRE	422	229	**54.3**	49.4	59.1								
			POST	423	407	**96.2**	93.9	97.8	422	328	**77.7**	73.4	81.6	**8.3**	7.5	9.2
		3-8 primed	PRE	81	40	**49.4**	38.1	60.7								
			POST	81	74	**91.4**	83.0	96.5	81	48	**59.3**	47.8	70.1	**5.5**	4.4	6.9
		9-17 primed	PRE	297	140	**47.1**	41.3	53.0								
			POST	297	292	**98.3**	96.1	99.5	297	199	**67.0**	61.3	72.3	**7.1**	6.2	8.1
	D-QIV-Y	overall	PRE	232	34	**14.7**	10.4	19.9								
			POST	234	169	**72.2**	66.0	77.9	232	159	**68.5**	62.1	74.5	**10.4**	9.0	11.9
B/Brisbane/60/2008 (Victoria)	D-QIV	3-8 unprimed	PRE	410	171	**41.7**	36.9	46.6								
			POST	411	400	**97.3**	95.3	98.7	410	317	**77.3**	73.0	81.3	**9.8**	8.7	11.0
		3-8 primed	PRE	78	46	**59.0**	47.3	70.0								
			POST	78	78	**100**	95.4	100	78	47	**60.3**	48.5	71.2	**4.9**	3.9	6.3
		9-17 primed	PRE	302	164	**54.3**	48.5	60.0								
			POST	302	292	**96.7**	94.0	98.4	302	189	**62.6**	56.9	68.1	**6.7**	5.8	7.8
	FLUARIX	3-8 unprimed	PRE	429	169	**39.4**	34.7	44.2								
			POST	428	409	**95.6**	93.2	97.3	428	327	**76.4**	72.1	80.3	**10.1**	9.0	11.4
		3-8 primed	PRE	82	49	**59.8**	48.3	70.4								
			POST	82	80	**97.6**	91.5	99.7	82	40	**48.8**	37.6	60.1	**4.3**	3.4	5.3
		9-17 primed	PRE	308	178	**57.8**	52.1	63.4								
			POST	308	301	**97.7**	95.4	99.1	308	193	**62.7**	57.0	68.1	**6.6**	5.7	7.6
	TIV-2	3-8 unprimed	PRE	422	179	**42.4**	37.7	47.3								
			POST	423	306	**72.3**	67.8	76.6	422	137	**32.5**	28.0	37.2	**3.0**	2.7	3.3
		3-8 primed	PRE	81	53	**65.4**	54.0	75.7								
			POST	81	72	**88.9**	80.0	94.8	81	17	**21.0**	12.7	31.5	**2.3**	1.8	2.9
		9-17 primed	PRE	297	167	**56.2**	50.4	62.0								
			POST	297	261	**87.9**	83.6	91.4	297	83	**27.9**	22.9	33.4	**2.4**	2.1	2.7
	D-QIV-Y	overall	PRE	232	28	**12.1**	8.2	17.0								
			POST	234	167	**71.4**	65.1	77.1	232	158	**68.1**	61.7	74.1	**9.7**	8.5	11.2

					SPR					SCR				MGI		
							95% CI					95% CI			95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL	N	n	%	LL	UL	Value	LL	UL
B/Brisbane/3/2007 (Yamagata)	D-QIV	3-8 unprimed	PRE	410	253	**61.7**	56.8	66.4								
			POST	411	407	**99.0**	97.5	99.7	410	323	**78.8**	74.5	82.6	**9.6**	8.6	10.8
		3-8 primed	PRE	78	62	**79.5**	68.8	87.8								
			POST	78	78	**100**	95.4	100	78	53	**67.9**	56.4	78.1	**5.6**	4.3	7.3
		9-17 primed	PRE	302	250	**82.8**	78.0	86.9								
			POST	302	300	**99.3**	97.6	99.9	302	197	**65.2**	59.6	70.6	**5.6**	4.9	6.3
	FLUARIX	3-8 unprimed	PRE	429	253	**59.0**	54.2	63.7								
			POST	428	387	**90.4**	87.2	93.0	428	178	**41.6**	36.9	46.4	**3.3**	3.0	3.6
		3-8 primed	PRE	82	56	**68.3**	57.1	78.1								
			POST	82	78	**95.1**	88.0	98.7	82	25	**30.5**	20.8	41.6	**2.5**	2.1	2.9
		9-17 primed	PRE	308	266	**86.4**	82.0	90.0								
			POST	308	307	**99.7**	98.2	100	308	100	**32.5**	27.3	38.0	**2.5**	2.3	2.8
	TIV-2	3-8 unprimed	PRE	422	266	**63.0**	58.2	67.7								
			POST	423	422	**99.8**	98.7	100	422	350	**82.9**	79.0	86.4	**10.9**	9.7	12.3
		3-8 primed	PRE	81	63	**77.8**	67.2	86.3								
			POST	81	81	**100**	95.5	100	81	53	**65.4**	54.0	75.7	**5.9**	4.5	7.6
		9-17 primed	PRE	297	264	**88.9**	84.8	92.2								
			POST	297	295	**99.3**	97.6	99.9	297	163	**54.9**	49.0	60.6	**4.9**	4.3	5.6
	D-QIV-Y	overall	PRE	232	48	**20.7**	15.7	26.5								
			POST	234	212	**90.6**	86.1	94.0	232	191	**82.3**	76.8	87.0	**12.9**	11.0	15.3

D-QIV = Subjects of 3-17 years received D-QIV *Fluarix* = Subjects of 3-17 years received *Fluarix* (contained the B Victoria strain) TIV-2 = Subjects of 3-17 years received TIV-2 (contained the B Yamagata strain) D-QIV-Y = Subjects of 6-35 months received D-QIV 3-8 unprimed = Unprimed subjects of 3-8 years of age 3-8 primed = Primed subjects of 3-8 years of age, 9-17 primed = Primed subjects of 9-17 years of age, N = Number of subjects with available results, n/% = Number/percentage of seroprotected subjects (HI titer ≥ 40 1/DIL)

Rapporteur's comment:
As for seropositivity analyses discussed before pre-vaccination seroprotection rates and immunological responses to vaccination are by and large similar across all paediatric age groups, regardless of pre-vaccination serostatus (except those from 6 – 35 months of age, D-QIV-Group). Seroconversion rates and mean geometric are increasing, however, lower SCRs and MGIs observed occasionally are mainly due to extremely high pre-vaccination HI titers being close to or reaching a plateau level already before vaccination.

Table 5: Study D-QIV-003: Seropositivity rates, GMTs and vaccine response rates for neutralising antibodies at day 0 and day 28 or day 56, by priming status and by age (3-8/9-17 years) (ATP cohort for immunogenicity for MN subset)

					≥ 1:28				GMT			Vaccine response			
							95% CI			95% CI				95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL	n	%	LL	UL
A/California/7/2009 (H1N1)	D-QIV	3-8 unprimed	PRE	47	34	**72.3**	57.4	84.4	**75.7**	51.7	111.0				
			POST	47	47	**100**	92.5	100	**1096.4**	656.7	1830.4	40	**85.1**	71.7	93.8
		3-8 primed	PRE	10	8	**80.0**	44.4	97.5	**132.7**	44.7	393.8				
			POST	10	9	**90.0**	55.5	99.7	**1107.1**	317.2	3864.5	7	**70.0**	34.8	93.3
		9-17 primed	PRE	35	27	**77.1**	59.9	89.6	**70.1**	46.8	105.0				
			POST	35	35	**100**	90.0	100	**1084.2**	615.4	1910.3	31	**88.6**	73.3	96.8
	FLUARIX	3-8 unprimed	PRE	46	29	**63.0**	47.5	76.8	**75.0**	49.3	114.2				
			POST	46	45	**97.8**	88.5	99.9	**1015.9**	577.0	1788.6	38	**82.6**	68.6	92.2
		3-8 primed	PRE	12	11	**91.7**	61.5	99.8	**100.6**	62.3	162.5				
			POST	12	12	**100**	73.5	100	**1158.6**	459.3	2922.6	9	**75.0**	42.8	94.5
		9-17 primed	PRE	37	33	**89.2**	74.6	97.0	**99.8**	73.6	135.3				
			POST	37	37	**100**	90.5	100	**1121.3**	709.0	1773.5	28	**75.7**	58.8	88.2
A/Victoria/210/2009 (H3N2)	D-QIV	3-8 unprimed	PRE	47	36	**76.6**	62.0	87.7	**82.1**	56.4	119.4				
			POST	47	47	**100**	92.5	100	**541.7**	368.2	797.0	27	**57.4**	42.2	71.7
		3-8 primed	PRE	10	9	**90.0**	55.5	99.7	**69.7**	27.5	176.8				
			POST	10	10	**100**	69.2	100	**247.6**	100.7	609.2	3	**30.0**	6.7	65.2
		9-17 primed	PRE	35	34	**97.1**	85.1	99.9	**97.3**	69.2	136.9				
			POST	35	35	**100**	90.0	100	**712.4**	448.7	1131.2	21	**60.0**	42.1	76.1
	FLUARIX	3-8 unprimed	PRE	46	42	**91.3**	79.2	97.6	**144.7**	98.7	212.3				
			POST	46	46	**100**	92.3	100	**883.8**	586.3	1332.4	26	**56.5**	41.1	71.1
		3-8 primed	PRE	12	12	**100**	73.5	100	**111.0**	68.0	181.3				
			POST	12	12	**100**	73.5	100	**527.4**	290.3	958.1	7	**58.3**	27.7	84.8
		9-17 primed	PRE	37	34	**91.9**	78.1	98.3	**74.9**	55.4	101.3				
			POST	37	37	**100**	90.5	100	**245.4**	169.9	354.4	12	**32.4**	18.0	49.8

					≥ 1:28				GMT			Vaccine response			
							95% CI			95% CI				95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL	n	%	LL	UL
B/Brisbane/60/2008 (Victoria)	D-QIV	3-8 unprimed	PRE	47	18	**38.3**	24.5	53.6	**26.5**	20.4	34.4				
			POST	47	45	**95.7**	85.5	99.5	**185.7**	122.4	281.6	25	**53.2**	38.1	67.9
		3-8 primed	PRE	10	7	**70.0**	34.8	93.3	**33.2**	20.6	53.6				
			POST	10	10	**100**	69.2	100	**183.7**	76.9	438.6	3	**30.0**	6.7	65.2
		9-17 primed	PRE	35	24	**68.6**	50.7	83.1	**46.0**	32.4	65.3				
			POST	35	35	**100**	90.0	100	**249.8**	180.6	345.4	17	**48.6**	31.4	66.0
	FLUARIX	3-8 unprimed	PRE	46	19	**41.3**	27.0	56.8	**28.0**	21.1	37.1				
			POST	46	42	**91.3**	79.2	97.6	**165.7**	106.8	257.0	18	**39.1**	25.1	54.6
		3-8 primed	PRE	12	5	**41.7**	15.2	72.3	**30.9**	15.5	61.8				
			POST	12	10	**83.3**	51.6	97.9	**106.7**	48.6	234.3	3	**25.0**	5.5	57.2
		9-17 primed	PRE	37	24	**64.9**	47.5	79.8	**45.6**	32.0	64.9				
			POST	37	36	**97.3**	85.8	99.9	**191.2**	140.2	260.9	18	**48.6**	31.9	65.6
B/Brisbane/3/2007 (Yamagata)	D-QIV	3-8 unprimed	PRE	47	20	**42.6**	28.3	57.8	**26.7**	20.9	34.0				
			POST	47	45	**95.7**	85.5	99.5	**227.3**	163.8	315.4	33	**70.2**	55.1	82.7
		3-8 primed	PRE	10	5	**50.0**	18.7	81.3	**32.3**	14.2	73.4				
			POST	10	10	**100**	69.2	100	**156.4**	69.0	354.6	5	**50.0**	18.7	81.3
		9-17 primed	PRE	35	26	**74.3**	56.7	87.5	**68.8**	43.1	109.8				
			POST	35	34	**97.1**	85.1	99.9	**688.6**	455.6	1040.8	26	**74.3**	56.7	87.5
	FLUARIX	3-8 unprimed	PRE	46	16	**34.8**	21.4	50.2	**24.5**	18.9	31.9				
			POST	46	29	**63.0**	47.5	76.8	**47.5**	33.6	67.2	5	**10.9**	3.6	23.6
		3-8 primed	PRE	12	9	**75.0**	42.8	94.5	**33.5**	21.7	51.9				
			POST	12	12	**100**	73.5	100	**77.1**	40.4	147.0	2	**16.7**	2.1	48.4
		9-17 primed	PRE	37	32	**86.5**	71.2	95.5	**84.3**	57.4	123.8				
			POST	37	34	**91.9**	78.1	98.3	**264.1**	158.3	440.5	13	**35.1**	20.2	52.5

D-QIV = Subjects of 3-17 years received D-QIV; *Fluarix* = Subjects of 3-17 years received *Fluarix* (contained the B Victoria strain) , GMT = geometric mean antibody titre calculated on all subjects, 3-8 unprimed = Unprimed subjects 3-8 years of age 3-8 primed = Primed subjects 3-8 years of age, 9-17 primed = Primed subjects 9-17 years of age , N = number of subjects with available results, n/% = number/percentage of subjects with titre within the specified range, 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit, PRE = Pre-vaccination at Day 0; POST = Post-vaccination at 28 days after the last vaccination

Rapporteur's comment:
Pre-vaccination MN titres analysed in a subset of individuals from 3 to 17 years of age are even higher than pre-vaccination HI titers in both unprimed and primed individuals. Response rates following one dose (primed individuals) or two doses (unprimed individuals) are close to 100 % for any strain and any age group except response to Fluarix against the B/Yamagata lineage in unprimed individuals. Otherwise Fluarix causes unexpectedly high MN titers against the heterologous B/Yamagata lineage not contained in Fluarix.

- Safety results (D-QIV-003)

The rate of any local AE in subjects at the age of 3-17 was balanced between the vaccine groups (54.3%, 51.8% and 52.1% of subjects in the D-QIV, Fluarix and TIV-2 groups, respectively). The most frequently reported local AE in this study was injection site pain, reported in slightly higher rates in the D-QIV group (49.2% of subjects) compared to the Fluarix group (47.1% of subjects) and to the TIV-2 group (45.9% of subjects). These minor differences do not seem to be clinically relevant. There was no evidence of increased local reactogenicity following administration of the second dose compared to the first dose in unprimed subjects. The rate of grade 3 symptoms was low and comparable among the different vaccine groups.

In subjects aged 6 to 17 years, the most frequently reported solicited general AEs were fatigue 21.0%, 20.0% and 18.2% of subjects in the D-QIV, Fluarix and TIV-2 Groups), muscle aches (18.9%, 18.0% and 16.9%) and headache (17.9%, 21.2% and 18.2%). After administration of QIV the incidence of those solicited general AEs in this age group was in a similar rate compared to the rate of incidence in 18-64 year-old subjects. The median duration of solicited general AEs ranged between 1.0 and 2.0 days for the three groups.
Approximately 40% of the participants (QIV-003) received a second dose; after that, all three groups (QIV, Fluarix and TIV-2) showed a decrease of solicited general AEs.

A higher incidence of fever after administration of QIV in children at the age of 3 to 5 compared to the older children (6-18 years of age) has been found (overall/subject: 17.2% vs 7.8%, respectively). In children below of 3 years the rate of fever still increased (25.3% in 18 to 47 months age old). However, comparable rates were reported after the use of Fluarix or TIV-2 in children at an age of 3 to 5 and this is in line with previous findings in clinical studies with influenza vaccines in this age group.
Loss of appetite, irritability and drowsiness occurred slightly more often in the QIV group compared to the trivalent vaccines. They were reported by 20.3 % to 23.0 % of the subjects in the QIV group but only by 12.7 % to 21.1% (overall/subject) of the subjects in the Fluarix or TIV-2 group. Solicited general AEs of grade 3 intensity were reported for 1.0 %-1.7 % in the QIV group and for 0.6 % - 1.1% of the subjects 3 to 5 years old in the control groups. The median duration of solicited general AEs ranged between 1.0 and 3.0 days (1.0 and 3.0 days for the D-QIV group and between 1.0 and 2.0 days for the Fluarix and TIV-2 groups).

As expected, in all vaccine groups (QIV, Fluarix and TIV-2) unsolicited AEs were reported in higher incidence in the paediatric population compared to adult (about 31.0%-33.8%. However, the incidences were balanced comparing the different vaccine groups. The most commonly reported unsolicited AEs in this age group were nasopharyngitis and upper respiratory tract infection. In all age groups and in all vaccine groups causally related AEs occurred in 1.8 to 2.6 % of subjects.

Vomiting was the most common grade 3 unsolicited AE in all vaccine groups (0.4- 0.7 %). Grade 3 AEs that were considered related to vaccination were reported by 1 subject in the QIV group (vomiting) and by 3 subjects in the TIV group (abdominal pain, vomiting, rhinorrhea).

Higher incidences of any unsolicited AEs within the 28 day postvaccination period were seen in the 3-8 years stratum compared to the older, 9-17 years age stratum (16.1% to 20.3% subjects in the 9-17 years stratum versus 39.0% to 41.4% of subjects in the 3-8 years group). This is not remarkable as younger children suffer from more infections than older ones.

The proportions of subjects of 3-17 years reporting at least one MAE (Medical Attended Events) within 28 days post vaccination were similar in the three vaccine groups (16.9%, 15.8% and 18.8% in the DQIV, Fluarix and TIV-2 groups, respectively). The most common MAE was related to nasopharyngitis (i.e. reported by 3.2% to 4.3% of subjects across groups).
For MAEs reported during the period up to study end at month 6, the incidence of MAEs was also similar among the 3 vaccine groups (29.6%, 30.5% and 33.3% of subjects, respectively).

Overall, three subjects discontinued the study due to AE/SAE (two were SAEs (one subject from the DQIV and one subject from the Fluarix group) and one (subject from the Fluarix group) was a non-serious AE). None of those were considered related to vaccination.
One 3-vear old child died after a road accident.

3. Discussion on clinical aspects FLU D-QIV-003

Integration of a second B strain into seasonal influenza vaccine formulations will undoubtedly increase overall vaccine efficacy since a significant factor contributing to mismatches between vaccine composition and circulating strains will be eliminated.
Unfortunately, understanding on the clinical mode of action of highly purified inactivated split or subunit influenza vaccines is rather cryptic being largely based on the relation between HI-titers and protection against a challenge dose of life virus of a well primed younger, healthy adult study population. Priming of this population was either achieved through natural exposure or vaccination using whole virion vaccines known to be much more immunogenic compared to the highly purified antigen preparations used nowadays. These investigations, dating back almost 4 decades by now are the basis for a surrogate parameter, namely an HI titer of ≥ 1:40, which is still used as a serological correlate predicting vaccine efficacy. While this might be the case for a naturally exposed population with sufficient baseline immunity not much is known for populations deviating from this ideal. For split and subunit vaccines it is unknown whether these are able to prime previously unexposed individuals in the same way as it occurs through natural exposure (children) and whether these are still effective in elderly populations (with and without acute and/or chronic disease(s)) who on the one hand should benefit from high levels of residual immunity, but on the other hand suffer from a less flexible while aging immune system which is no longer able to effectively respond to seasonally updated vaccine antigens. Both presumptions may explain why overall vaccine efficacy in the very young as well as in the very old is rather poor.
Nevertheless, concerns on the specificity of both, HI- and VN- tests used to measure serological responses in the various clinical studies performed using D-QIV in comparison to Fluarix indicate that vaccine efficacy extrapolated from test readouts might be overestimated for all age groups.
However, all these concerns are also applicable to any other seasonal influenza vaccine licensed in the EU (and beyond) since the regulatory system applicable to these vaccines always has and still is supporting the approaches chosen by the MAA. Moreover, issues raised on the appropriateness of serological test systems cannot be abolished without establishing an institutionalised system which is able to calibrate serological test readouts against reference preparations definitely proven to correlate with vaccine efficacy. No such system is currently in

place which indicates regulatory inactivity and failure rather than deficiencies in the clinical development program by the companies.
After all, raising doubts on the test and control vaccines described in this assessment report would mean to also raise doubts on the usefulness of any other inactivated seasonal influenza vaccine licensed and used in the EU and worldwide.

Rapporteur´s comment:
Fluarix, administered in children 3-17 years of age (N=912) in study FLU-D-QIV-003, was shown to be generally well- tolerated and to be sufficiently immunogenic taking into account the EU-guideline.
However, the safety data obtained in this trial are not in line with the current approved Fluarix SmPC/PL (point 4.8), e.g. fatigue, fever, muscle ache or other adverse events in this study are very common in children and therefore does this new safety data warrant a change of the SmPC.

FLU D-QIV-AS03-005 (EUdraCT-2010-020330-26)

- **Description**

A phase IIa, observer-blind, multi-country, multi-centre, randomised study to evaluate the immunogenicity, safety and reactogenicity of the GSK quadrivalent influenza vaccine (QIV) adjuvanted with various doses of ASO3, administered in children aged 6 to 35 months, and compared to non-adjuvanted QIV and Fluarix.
This study had been designed to identify the optimal formulation (combination of HA dosage and ASO3 dosage) of the FLU D-QIV-ASO3 vaccine compared to the non-adjuvanted QIV, given intramuscularly in children aged 6-35 months.

- **Methods**

The study planned to evaluate six combinations of three dosages of antigen with two adjuvant ASO3 dosages. Two non-adjuvanted control arms were also to be evaluated: one with D-QIV and one with Fluarix.

- **Results**

During regular monitoring of the clinical lots of the adjuvanted QIV produced for this study, it became apparent that the N1H1v antigen content declined slightly. At month 3 time point the observed concentrations for H1N1v haemagglutinin were confirmed to be below the product specifications. Therefore GSK precluded further administration of the adjuvanted quadrivalent candidate vaccine. As a consequence, enrolment was stopped.

Four subjects who had already been enrolled in the study were followed for safety until Day 180. Of the 4 subjects enrolled, one received Fluarix.

HI antibody titres after administration of Fluarix were not evaluated, safety was assessed. No local and general solicited symptoms were reported for the subject. Of the 3 unsolicited symptoms reported (HZ, bronchitis and fever) for the subjects none of these were assessed as causally related to Fluarix.

Discussion on clinical aspects on FLU D-QIV-AS03-005

Due to the fact that only one subject was evaluated in this study, the data obtained here are not relevant to warrant any change to the approved Fluarix SmPC/PL.

FLU Q-QIV-003 PRI (EUdraCT number: 2010-021073-36)

- **Description/Title**

A phase III, double blind, randomized study to evaluate the immunogenicity and safety of GSK Biological´quadrivalent influenza candidate vaccine, FLU Q-QIV, compared to GSK Biologicals´ trivalentinfluenza vaccine Fluarix administered intramuscularly to children 3-17 years of age; and to describe the safety and immunogenicity of FLU-Q-QIV in children 6-35 months of age.
Study centers:
This was a multi-center study conducted at 32 centers across Canada, Mexico, Spain, Taiwan, and the United States.

- **Methods**

The purpose of this study was to assess, in subjects 3 to 17 years old, non-inferiority of the quadrivalent FLU Q-QIV vaccine compared to trivalent *Fluarix*-VB (TIV-VB), and *Fluarix*-YB (TIV-YB) with respect to the immunogenicity of the shared virus strains and immunological superiority of FLU Q-QIV compared to *Fluarix*-VB with respect to the Yamagata B lineage strain and to *Fluarix*-YB with respect to the Victoria B lineage strain. The study design relied on FDA/CBER guidance on statistical criteria for immunological endpoints and recommendation for comparison to a US-licensed seasonal inactivated influenza vaccine to infer immunogenic non-inferiority. In addition, a descriptive evaluation of the safety and immunogenicity of FLU Q-QIV was made in younger children (6 to 35 months old) in a separate and independent arm of the study.

- Objectives

Primary:

1. To test the immunogenic non-inferiority (in terms of Geometric Mean Titer [GMT] and Seroconversion Rate [SCR]) for the shared viral strains of FLU Q-QIV versus *Fluarix*-VB (TIV containing Victoria B strain) and *Fluarix*-YB (TIV containing Yamagata B strain) in children 3 to 17 years old approximately 28 days after completion of dosing (approximately at Day 28 for primed subjects and approximately at Day 56 for unprimed subjects).

Criteria (based on FDA/CBER guidance) to conclude non-inferiority:
The test of non-inferiority was based on the analysis of the entire 3 to 17 year-old age range in each treatment group, and immunogenic non-inferiority was concluded if:

- The upper limit of the two-sided 95% confidence interval of the GMT ratio (*Fluarix*/FLU QQIV) after completion of the vaccination series did not exceed 1.5 for the three strains (H3N2, H1N1 and shared B, i.e., VB or YB), AND
- The upper limit of the two-sided 95% confidence interval for the difference in SCR (*Fluarix* minus FLU Q-QIV) did not exceed 10% for the three strains contained in each *Fluarix* vaccine (TIV-VB and TIV-YB)

Secondary:

1. To test the immunogenic superiority of the B strains present in FLU Q-QIV (in terms of GMT ratio and SCR) in children 3 to 17 years old approximately 28 days after completion

of dosing (approximately at Day 28 for primed subjects; approximately at Day 56 for unprimed subjects) by comparing:
- FLU Q-QIV to *Fluarix*-YB (i.e., TIV-YB) with respect to the Victoria lineage B strain, and
- FLU Q-QIV to *Fluarix*-VB (i.e., TIV-VB) with respect to the Yamagata lineage B strain

Criteria to conclude superiority:
The test of immunogenic superiority was based on the analysis of the entire 3 to 17 year-old age range in each treatment group, and immunogenic superiority was concluded if the lower limit of the two-sided 95% confidence interval on GMT ratio (FLU Q-QIV/*Fluarix*) was greater than 1.5 and the difference in SCR (FLU Q-QIV minus *Fluarix*) was greater than 10%.
To describe the immunogenicity (in terms of Geometric Mean Titer [GMT], seroprotection rate [SPR], seroconversion rate [SCR] and seroconversion factor [SCF]) of FLU Q-QIV and each *Fluarix* vaccine overall, and for the age categories 3 to 8 years and 9 to 17 years, and of FLU-QQIV for the 6-35 month age group.
To evaluate fulfilment of CBER immunogenicity criteria by the immune response to the second, Yamagata lineage, B strain in FLU Q-QIV (in 3-17 year olds).
(FDA/CBER criteria were considered met if the lower limit of 95% CI for SCR was ≥40% and postvaccination SPR was ≥70%).

To evaluate and describe the reactogenicity and safety of FLU Q-QIV and each *Fluarix* vaccine overall in the 3 to 17 years age category and for the age categories 3 to 8 years and 9 to 17 years.
The reactogenicity and safety of FLU-Q-QIV for the 6-35 month age group were also described.
The following reactogenicity and safety analyses were performed:
- Solicited local symptoms during the 7-day post-vaccination follow-up (day of vaccination and 6 subsequent days) overall (3-17 years) and in three age groups (6 to 35 months, 3-8 years, 9-17 years).
- Solicited general symptoms during the 7-day post-vaccination follow-up (day of vaccination and 6 subsequent days) overall (3-17 years), and for the 6 to 35 months, 3 to 4 year, 5 to 8 year and 9 to 17 year-old age groups (note that the 3-4 year-old and 5-8 year-old groups are assessed using different solicited general symptoms because of their differential reporting abilities, and are thus analyzed separately for this category).
- Unsolicited symptoms during the 28-day (day of vaccination and 27 subsequent days) postvaccination follow-up period overall (3-17 years), and in the 6 to 35 months, 3-8 years and 9-17 years age groups.
- Serious adverse events (SAEs), medically attended adverse events (MAEs) and potential immunemediated diseases (pIMDs) during the entire study period (Day 0 to Day 180 after the first vaccination), overall (3-17 years), and in the 6 to 35 months, 3-8 years and 9-17 years age groups.

- Study design

Randomized (1:1:1) in three treatment groups (FLU Q-QIV, *Fluarix*-VB, and *Fluarix*-YB), age stratified (1:1 into 2 age strata, 3-8 years old, and 9-17 years old), multi-center study (multicountry), with a double-blind design for the comparison of FLU Q-QIV to each *Fluarix* TIV in 3 to 17 year-old subjects and open-label for the descriptive evaluation of FLU Q-QIV in 6 to 35 monthold subjects (independent and stand-alone arm which did not contribute any data to the analysis of the three blinded arms of the study).

- Study population /Sample size

Male or female children 6 months to 17 years of age who were in stable health at the time of the first vaccination .

Planned: Total: **3000**: QIV1: **900**; TIV-VB: **900**; TIV-YB: **900**; QIV2: **300**
QIV1=FLU Q-QIV (3-17 years of age), TIV-VB=*Fluarix*-VB (3-17 years of age); TIV-YB=*Fluarix*-YB (3-17 years of age); QIV2=FLU Q-QIV (6-35 months of age)

- Treatments

Vaccination schedule: One intramuscular (IM) injection at Day 0 for primed subjects and two IM injections, one at Day 0 and one at Day 28 for unprimed subjects.
Primed subjects: Subjects ≥ 9 years of age and any subjects 6 months to 8 years of age who had received at least one dose of an influenza A [H1N1] 2009 monovalent vaccine in the last season [or had laboratory confirmed H1N1 infection] AND have received two doses of seasonal influenza vaccine separated by at least one month during the last season or had received at least one dose prior to last season.
Unprimed subjects: Subjects 6 months to 8 years of age who had not received any influenza A [H1N1] 2009 monovalent vaccine in the previous season [or did not have laboratory confirmed H1N1 infection] OR who had not received any seasonal influenza vaccine in the past or received only one dose for the first time in the last influenza season.

Immunogenicity sampling: Blood samples were collected at Days 0 and 28 for primed subjects and Days 0 and 56 for unprimed subjects.

The study duration was to be approximately 6 months for all subjects.

- Outcomes/endpoints

Immunogenicity:
Humoral immune response to each of the influenza vaccine strains in each vaccine group (FLU QQIV and each TIV in 3-17 year olds). Measurement of serum Hemagglutination Inhibiting (HI) antibody titer against each strain at pre-vaccination (Day 0) and at post-vaccination (Day 28 for primed or Day 56 for unprimed subjects).

- Primary endpoints included the following parameters (with 95% confidence intervals [CIs]) which were calculated for all subjects in each treatment group: GMTs of HI antibody titers and SCRs for each strain at Day 28 after the last vaccine dose in each treatment group.
- Secondary endpoints to further assess humoral immune response included the following parameters (with 95% CIs) which were calculated for all subjects and for the 6 to 35 months, 3-8 years and 9-17 years old age groups: Geometric mean reciprocal serum HI antibody titers and SPRs against each of the vaccine strains in each group at Day 0 and at Day 28 after the last vaccine dose, and SCRs and SCFs for the vaccine strains at Day 28 after the last vaccine dose in each treatment group.

Safety/reactogenicity:

- Recording of incidence rate, duration, and intensity of solicited local adverse events (pain, redness, and swelling at injection site for all subjects) during a 7-day follow-up period (Day 0 to Day 6) after each vaccination in each treatment group.
- Recording of incidence rate, duration, intensity, and relationship to vaccination of solicited general adverse events (fever, irritability/fussiness, drowsiness, loss of appetite in subjects <5 years of age and fatigue/tiredness, fever, headache, joint pain, generalized/widespread muscle aches, and shivering in subjects □5 years of a a 7-day follow-up period (Day 0 to Day 6) after each vaccination in each treatment group.

- Recording of incidence rate, intensity, and relationship to vaccination of unsolicited adverse events during a 28-day follow-up (Day 0 to Day 27) after each vaccination in each treatment group.
- Recording of Serious Adverse Events (SAEs), Medically Attended Adverse Events (MAEs), and potential immune-mediated diseases (pIMDs) in each treatment group during the entire study period (i.e, day of first vaccination and 180 subsequent days).

Statistical Methods
Demographic characteristics (age, gender, and ethnicity/geographic ancestry) were analyzed for each study cohort.
Analysis of immunogenicity was performed on the ATP cohort (primary analysis) and on the Total vaccinated cohort (complementary analysis) since the percentage of vaccinated subjects eliminated (6.7%) from the ATP cohort exceeded 5%.
Analysis of safety/reactogenicity was performed on the Total vaccinated cohort.

- **Results Q-QIV-003**

- Recruitment/ Number analysed

Enrolled: Total: **3109**; QIV1: **932**; TIV-VB: **929**; TIV-YB: **932**; QIV2: **302**; Not vaccinated: **15**

*Total vaccinated cohort, TVC (Safety analysis):*Total: **3094**; QIV1: **932**; TIV-VB: **929**; TIV-YB: **932**; QIV2: **301**

ATP Immunogenicity cohort, ATP-I (Immunogenicity analysis): Total: **2886**; QIV1: **878**; TIV-VB: **871**; TIV-YB: **878**; QIV2: **259**

Completed (6-month Safety follow up): Total: **2960**; QIV1: **894**; TIV-VB: **889**; TIV-YB: **902**; QIV2: **275**

- Baseline data

The demographic profiles were comparable across the three treatment groups (QIV1, TIV-VB, and TIV-YB in subjects 3 to 17 years old) with respect to mean age, gender and racial distribution. The mean age of subjects was 8.9 years in each treatment group. In total, 51.6% of subjects were male and 48.4 % were female. The population was predominantly White/Caucasian (62.8%). For the QIV2 group (6 to 35 months of age), the mean age of subjects was 1.2 years. In total, 52.5% of subjects were male and 47.5 % were female. The population was predominantly White/Caucasian (68.4%).

The immunogenicity analyses were performed on the ATP cohort (primary analysis) and on the Total vaccinated cohort (supplemental analysis) since the percentage of vaccinated subjects eliminated (6.7%) from the ATP cohort exceeded 5%.

- Immunogenicity results of Q-QIV-003 PRI

The study met its confirmatory primary objective of demonstrating immunogenic non-inferiority of the quadrivalent FLU Q-QIV vaccine compared to the trivalent *Fluarix* vaccines, TIV-VB (*Fluarix* containing Victoria B strain) or TIV-YB (*Fluarix* containing Yamagata B strain) after completion of the vaccination series in children 3 to 17 years of age.

Table 6: Non-inferiority of FLU Q-QIV (QIV1) versus *Fluarix*-VB (TIV-VB) and *Fluarix*-YB (TIV-YB) in terms of adjusted GMT ratios of HI antibody post-last vaccination for each of the four QIV strains (non-inferiority criterion: adjusted GMT ratio UL of 95% CI ≤ 1.5) (ATP-I)

					Adjusted GMT ratio (TIV-VB+TIV-YB / QIV1)		
	TIV-VB+TIV-YB		QIV1			95% CI	
Antibody	N	Adjusted GMT	N	Adjusted GMT	Value	LL	UL
A/California/7/2009 (H1N1)	1747	421.4	876	366.3	1.15	1.06	1.25
A/Victoria/210/2009 (H3N2)	1746	144.3	876	145.8	0.99	0.92	1.07
					Adjusted GMT ratio (TIV-VB / QIV1)		
	TIV-VB		**QIV1**			**95% CI**	
Antibody	**N**	**Adjusted GMT**	**N**	**Adjusted GMT**	**Value**	**LL**	**UL**
B/Brisbane/60/2008	870	243.4	876	252.5	0.96	0.87	1.07
					Adjusted GMT ratio (TIV-YB / QIV1)		
	TIV-YB		**QIV1**			**95% CI**	
Antibody	**N**	**Adjusted GMT**	**N**	**Adjusted GMT**	**Value**	**LL**	**UL**
B/Florida/4/2006	877	564.6	876	525.2	1.08	0.99	1.16

QIV1 = Flu Q-QIV (3 - 17 years) TIV-YB = Fluarix TIV Yamagata B strain (3 - 17 years) Adjusted GMT = geometric mean antibody titer adjusted for baseline titer N = Number of subjects with both pre- and post-vaccination results available 95% CI = 95% confidence interval for the adjusted GMT ratio (Ancova model: adjustment for baseline titer – pooled variance); LL = lower limit, UL = upper limit (Source: Study report Table 22-24, page93 and 94)

Table 7: Non-inferiority of FLU Q-QIV (QIV1) versus *Fluarix*-VB (TIV-VB) and *Fluarix*-YB (TIV-YB) in terms of seroconversion rate (difference in SCR) at day 28 for each of the four QIV strains (non-inferiority criterion: difference in SCR, UL of 95% CI ≤ 10%) (ATP-I)

							Difference in seroconversion rate (TIV-VB+TIV-YB minus QIV1)		
	QIV1			**TIV-VB+TIV-YB**				**95% CI**	
Antibody	**N**	**n**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**
A/California/7/2009	876	739	84.4	1747	1505	86.1	1.79	-1.04	4.77
A/Victoria/210/2009	876	614	70.1	1746	1200	68.7	-1.36	-5.05	2.41
							Difference in seroconversion rate (TIV-VB minus QIV1)		
	QIV1			**TIV-VB+TIV-YB**				**95% CI**	
Antibody	**N**	**n**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**
B/Brisbane/60/2008	876	653	74.5	870	622	71.5	-3.05	-7.21	1.12
							Difference in seroconversion rate (TIV-YB minus QIV1)		
	QIV1			**TIV-VB+TIV-YB**				**95% CI**	
Antibody	**N**	**n**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**
B/Florida/4/2006 (Yamagata)	876	659	75.2	877	644	73.4	-1.80	-5.89	2.30

TIV-VB+TIV-YB = Pooled TIV groups (3 - 17 years) QIV1 = Flu Q-QIV (3 - 17 years) Seronegative subjects (antibody titer < 10 1/DIL) prior to vaccination Seropositive subjects (antibody titer □10 1/DIL) prior to vaccination Seroconversion defined as:

For initially seronegative subjects, antibody titer □40 1/DIL after vaccination For initially seropositive subjects, antibody titer after vaccination □4-fold the pre-vaccination antibody titer N = Number of subjects with pre- and post-vaccination results available n/% = Number/percentage of seroconverted subjects 95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit (Source: Study report Table 25-27, page 94-95)

Both pre-defined statistical acceptance criteria for concluding immunogenic non-inferiority of all four strains in the FLU Q-QIV vaccine were met:

- the upper limit of the two-sided 95% confidence interval (CI) of the adjusted GMT ratio (*Fluarix*/FLU Q-QIV) was > 1.5 for each strain (A/H3N2, A/H1N1, VB and YB) contained in the FLU Q-QIV vaccine (Table 6) *and*,
- the upper limit of the two-sided 95% CI for the difference in SCR (*Fluarix* minus FLU QQIV) was >10% for each strain (A/H3N2, A/H1N1, VB and YB) contained in the FLU QQIV vaccine (Table 7).

The study met the confirmatory secondary objective of demonstrating immunogenic superiority of the quadrivalent FLU Q-QIV vaccine over the trivalent *Fluarix* vaccines, TIV-VB (with respect to the *Yamagata* lineage B strain) and TIV-YB (with respect to the *Victoria* lineage B strain) after completion of the vaccination series in children 3 to 17 years of age. Both pre-defined statistical acceptance criteria for inferring immunogenic superiority of QIV vs TIVs for the unique B strain in the QIV vs TIVs were met.
The study also achieved its confirmatory secondary objective of meeting CBER criteria for the additional B strain in the FLU Q-QIV vaccine administered to children 3 to 17 years of age.
The descriptive immunogenicity data (GMT, SCR, SPR, and SCF) indicated that, in children 6 to 35 months of age, each of the four strains in the FLU Q-QIV vaccine met CBER's SPR and SCR Criteria.

- Safety results Q-QIV-003 PRI

The safety analysis was performed on the Total vaccinated cohort (TVC). Since the percentage of vaccinated subjects excluded from the ATP cohort for analysis of safety (ATP-S) was less than 5% of the TVC, no secondary (complementary) analysis was performed on the ATP-S.
The results of the reactogenicity/safety analyses are summarized below.

Overall incidence of *solicited and unsolicited* AEs (overall/subject)

- *Any* solicited and unsolicited AEs were reported for 77.3%, 71.6%, and 69.0% of subjects in the QIV1, TIV-VB, and TIV-YB groups (3-17 years of age), respectively, and for 74.8% of subjects in the QIV2 group.

Solicited local AEs (overall/subject):

- Injection site pain was the most frequently reported local AE across all treatment groups with a lower incidence in children 6-35 months of age (reported for 69.8%, **59.0% and 59.2%** of 3-17 year-old subjects in the QIV1, **TIV-VB, TIV-YB** and 50.3% of 6-35 month-old subjects in the QIV2 groups, respectively).
- Grade 3 injection site pain was reported for 3.8%, 2.3%, 2.8%, and 2.0% of subjects in the QIV1, TIV-VB, TIV-YB, and QIV2 groups, respectively.

Solicited general AEs (overall/subject):

- Drowsiness (24.9%, **25.1%, and 27.0%** of subjects) and irritability (31.9%, **23.5%, and 25.4%** of subjects) were the most frequently reported general AEs across the three treatment groups (QIV1, **TIV-VB, and TIV-YB** groups, respectively) among subjects 3 to 5 years of age. In the QIV2 group (Q-QIV in subjects 6 to 35 months of age), irritability (48.3%) was the most frequently reported general AE, followed by drowsiness (34.9%), and loss of appetite (31.8%).

- Muscle ache (30.5%, **26.8%, and 26.6%** of subjects), fatigue (23.8%, **24.4%, and 24.4%** of subjects), and headache (23.4%, **23.6%, and 21.6%** of subjects) were the most frequently reported general AEs across the three treatment groups (Q-QIV, **TIV-VB, and TIV-YB** groups, respectively) in subjects 5 years of age and older.
- Grade 3 solicited general AEs, including fever, were reported with a very low incidence rate, ranging from 0.0% to 3.2% (in subjects 3 to <5 years of age) and 0.0% to 1.8% (in subjects >5 to 17 years of age).

Unsolicited AEs and MAEs (medically-attended adverse events):

- Among the 3 to 17 year-old subjects, 283 (30.4%) from the QIV1 group, 291 (31.3%) from the TIV-VB group, and 275 (29.5%) from the TIV-YB group reported at least one unsolicited adverse event (AE) during the 28-day post-vaccination period. In the QIV-only, 6 to 35 months old age group (QIV2), 160 subjects (53.2%) reported at least one unsolicited AE during the 28-day post-vaccination period. For all treatments and across both age groups, cough was the most frequently reported AE.
- Among the 3 to 17 year old subjects, 346 subjects (37.1%) from the QIV1 group, 335 (36.1%) from the TIV-VB group, and 350 (37.6%) from the TIV-YB group reported at least one MAE during the entire study period. In the QIV-only, 6 to 35 months old age group (QIV2), 147 subjects (48.8%) reported at least one MAE during the entire study period. For all treatments and across both age groups, upper respiratory tract infection was the most frequently reported MAE.

SAEs (Serious adverse events):

- No fatal SAEs were reported during the entire study period. Overall, 35 SAEs were reported in 21 subjects during the entire study period (out of a total vaccinated cohort of 3094 subjects).
- In subjects 3-17 years of age, two SAEs (angioedema and conjunctivitis) with onset on the day of vaccination reported for one subject (PID 5159, a 12-year old male subject) in the *Fluarix*-YB (TIV-YB) group were considered by the investigator to be related to the study vaccination. Both SAEs were reported to have recovered/resolved.
- In subjects 6-35 months of age, two SAEs (grand mal convulsion in PID 198, a 1-year old female subject with onset on the day of the first dose of Q-QIV; febrile convulsion in PID 3006, a 2-year old male subject with onset 18 days after first dose of Q-QIV) were also considered to be related to vaccination. Both SAEs were reported to have recovered/resolved.

Discussion on clinical aspects on FLU Q-QIV-003 PRI

Rapporteur's comment:
In conclusion, Fluarix administered in children 3-17 years of age (N=929) in study Q-QIV-003PRI, was shown to be generally well tolerated and immunogenic.
However, the safety data obtained in this study is not in line with the current approved Fluarix SmPC/PIL (point 4.8). As it is known from many other vaccines, in children the reactogenicity after vaccination is higher compared to the rate of adverse events after vaccination of adult or elderly. Consequently, this should be described in the SmPC.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

Target populations for seasonal influenza vaccination differ regionally in the EU, however, the key target populations for which most if not all Member States have specific recommendations, i.e. individuals with high risk factors such as acute or chronic underlying disease(s) were not included in immunogenicity and safety analyses.

No specific differences in immunological responses were found in infants, children and adolescents**.**
However, the rate of adverse events after vaccination is higher in children compared to adult or elderly. Consequently, this should be reflected in the SmPC.

- **Overall conclusion**

Data obtained in the 4 studies demonstrate immunogenicity being compliant with the current approved Fluarix SmPC/PI. However, the rate of adverse events in children is higher than mentioned in the current approved SmPC. Some adverse events, e.g. drowsiness, irritability, conjunctivitis or loss of appetite, are even missing in the SmPC.

- **Recommendation**

Based on the review of the paediatric data on safety and immunogenicity collected in the above mentioned studies the Rapporteur considers that the benefit-risk balance for Fluarix remains unchanged, however, the SmPC and PIL should be completed by the safety data obtained in children. As it is known from many other vaccines, in vaccinated children the reactogenicity is higher than in adult or elderly. This should be reflected in the SmPC.

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

The MAH should provide a proposal for wording of section 4.8 of the SmPC and section 4 of the PIL as mentioned in Section V (Rapporteur's Overall Conclusion and Recommendation).

Answer of the Applicant (21.01. 2013):

GSK acknowledge that the reactogenicity in the four studies, FLU D-QIV-002: DE/W/0054/pdWS/002, FLU D-QIV-003: DE/W/0054/pdWS/003, FLU D-QIV-AS03- 005: DE/W/0054/pdWS/004, FLU Q-QIV-003 PRI: DE/W/0054/pdWS/005, appears to be higher compared to reactogenicity observed in adults in other studies. However, these studies are conducted under widely varying conditions, such as during different time periods and in different countries, which may result in changes in medical practices over time and cultural differences in adverse event reporting. Therefore, it is difficult to compare the rates of reactogenicity in these studies, and cautious interpretation of the comparison is warranted.

However, the Company will update the SmPC (a) and the PIL(b) according to PEI recommendation:

a) With regard to the update of the current **SmPC** with some adverse events, the Company proposes to add a paediatric section and **update the wording of Section 4.8** as follow:

ADVERSE REACTIONS OBSERVED FROM CLINICAL TRIALS

Paediatric population

In three clinical studies healthy children 18 months to 17 years of age were administered Fluarix (more than 3500 children).The following adverse reactions have also been reported in this age population.

Organ class	Very common ≥1/10	Common ≥1/100, <1/10	Uncommon ≥1/1,000, <1/100
Metabolism and nutrition disorders	Lossofappetite[2]		
Psychiatric disorders	Irritability[2]		
Nervous system disorders	Drowsiness[2], headache[3]		
Gastrointestinal disorders		Gastrointestinal symptoms[3]	
Musculoskeletal, connective tissue and bone disorders	Jointpain[3],muscle aches[3]		
General disorders and administration site conditions	Fever[2],fatigue[3]. Localreactions: redness[1],swelling[1], pain[1]	Fever[3],shivering[3]	

1reported in children aged from 6 months to 17 years
2reported in children aged from 6 months to 5 years
3reported in children aged from 6 years to 17 years

ADVERSE REACTIONS REPORTED FROM POST-MARKETING SURVEILLANCE

Immune system disorders:
Allergic reactions (symptoms including conjunctivitis), in rare cases leading to shock, Angioedema

In three clinical studies healthy children 18 months to 17 years of age were administered Fluarix

b) With regard to the update of the current **PIL** with some adverse events (drowsiness, irritability, conjunctivitis or loss of appetite), the Company proposes to update the **wording of Section 4** as follow:

The following side effects have been reported during clinical trials in children and adolescents from 6 months to 17 years of age:

Very common (these may occur with more than 1 in 10 doses of the vaccine):

- irritability[1]
- loss of appetite[1]
- drowsiness[1]
- headache
- joint pain
- muscle aches
- fever[2]
- fatigue
- local reactions: redness, swelling, pain

[1] reported in children 6 months to 5 years of age
[2] common in children 6 years to 17 years of age

Common (these may occur with up to 1 in 10 doses of the vaccine):

- gastrointestinal symptoms
- shivering

Next to the above common side effects, the following side effects occurred after the vaccine came on the market:

- allergic reactions: discharge with itching of the eyes and crusty eyelids (conjunctivitis)

Rapporteur's comment:
The MAH provided a proposal for an updated wording of section 4.8 of the SmPC and section 4 of the PIL. In general, the wording is accepted. However, the age range of 18 months to 17 years in section 4.8 of the SmPC is not understood. Correct would be: "… healthy children from 6 months to 17 years of age".
Providing that the age range "6 months to 17 years" is agreed by the Applicant the issue is solved.

<u>During the procedure the following comment (FR) has been obtained (29. 3.2013):</u>

The proposed patient leaflet (PL) should be in line with the wording of the SmPC.
For example: in the SmPC, headache/joint pain are indicated as very common in children aged from 6 years to 17 years, while in the PL headache/joint pain are indicated as very common in children aged from 6 months to 17 years.

In response the MAH amended the Fluarix PIL as suggested (08.04.2013):

The following side effects have been reported during clinical trials in children and adolescents from 6 months to 17 years of age:

Very common (these may occur with more than 1 in 10 doses of the vaccine):

- irritability[2]
- loss of appetite[2]
- drowsiness[2]
- headache[3]
- joint pain[3]
- muscle aches[3]
- fever[2]
- fatigue[3]
- local reactions: redness[1], swelling[1], pain[1]

Common (these may occur with up to 1 in 10 doses of the vaccine):

- gastrointestinal symptoms[3]
- shivering[3]
- fever[3]

[1] reported in children 6 months to 17 years of age
[2] reported in children 6 months to <6 years of age
[3] reported in children 6 years to 17 years of age

Rapporteur's comment:
The MAH submitted a sufficient wording for the SmPC and the PIL.
Issue is solved.