



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Influenza virus haemagglutinin inactivated split influenza vaccine

Proprietary Product Name: Fluarix Tetra

Sponsor: GlaxoSmithKline Australia Pty Ltd

February 2014

TGA Health Safety
Regulation

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List of abbreviations

Abbreviation	Meaning
ANCOVA	Analysis of co variance
ATP	According to protocol
CBER	Center for Biologics Evaluation and Research
CDC	Center for Disease Control and Prevention USA
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
D-QIV	GSK's candidate quadrivalent influenza vaccine
ECDC	European Centre for Disease Control and Prevention
GMT	Geometric mean Titre
HI	Haemagglutination Index
LL	Lower limit
MGI	Mean Geometric Increase
RT-PCR	Reverse transcriptase-polymerase chain reaction
SAE	Serious adverse event
SCF	Sero conversion factor
SCR	Seroconversion rate
SPR	Seroprotection rate
TIV	Trivalent inactivated influenza vaccine
WHO	World Health Organization

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New Chemical/Biological Entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	21 August 2013
<i>Active ingredient:</i>	Influenza virus haemagglutinin inactivated split influenza vaccine ¹
<i>Product name:</i>	Fluarix Tetra
<i>Sponsor's name and address:</i>	GlaxoSmithKline Australia Pty Ltd 436-438 Johnston St, Abbotsford, VIC 3067
<i>Dose form:</i>	Suspension for Injection
<i>Strength:</i>	Influenza virus Haemagglutinin 15 µg/strain/dose
<i>Container:</i>	Pre-filled syringe
<i>Pack sizes:</i>	1 x 0.5 mL dose 10 x 0.5 mL dose
<i>Approved therapeutic use:</i>	<p><i>Fluarix Tetra is a quadrivalent vaccine indicated for active immunisation of adults and children from 3 years of age for the prevention of influenza disease caused by the influenza virus types A and B contained in the vaccine.</i></p> <p><i>The use of Fluarix Tetra should be based on official recommendations.</i></p>
<i>Route of administration:</i>	Intramuscular (IM)
<i>Dosage:</i>	<p>Fluarix Tetra should be administered as a single 0.5 ml injection. Children 3 years to less than 9 years of age who have not previously been vaccinated against influenza should receive a second dose of 0.5 ml after an interval of at least 4 weeks.</p> <p>Vaccination should be carried out by intramuscular injection preferably into the deltoid muscle or anterolateral thigh (depending on the muscle mass).</p>
<i>ARTG number:</i>	200674 and 210806

¹ Influenza virus Hemagglutinin Influenza A, inactivated, split (H1N1, H3N2) Influenza virus Hemagglutinin Influenza B, inactivated, split (B) (Yamagata/16/88 and Victoria/2/87 lineages)

Product background

This AusPAR describes the application by GlaxoSmithKline Australia Pty Ltd (GSK) to register a new influenza vaccine, Fluarix Tetra.

The sponsor proposed the following indication for Fluarix Tetra:

Fluarix Tetra is a quadrivalent vaccine indicated for active immunisation of adults and children from 3 years of age for the prevention of influenza disease caused by the influenza virus types A and B contained in the vaccine.

The use of Fluarix Tetra should be based on official recommendations.

Fluarix Tetra is a quadrivalent, split-virion, inactivated seasonal influenza vaccine and it contains antigens from two influenza A subtype viruses (subtypes H1N1 and H3N2) and two type B viruses (from two lineages, represented by B/Victoria/2/87 and B/Yamagata/16/88 strains). The formulation utilises the same starting materials and manufacturing and control processes, equipment and facilities, as currently licensed for the Fluarix trivalent vaccine. Fluarix Tetra is presented as a suspension for injection, in single use, pre-filled syringes.

The rationale for the development of quadrivalent influenza vaccine (QIV) is that while annual influenza vaccination is the most effective method of prevention of influenza to date, the current trivalent influenza vaccine includes only one of the two influenza B phylogenetic lineages. The addition of a second B strain aims to overcome the uncertainty in predicting the appropriate strain (the influenza vaccine strains are selected at least 6 months in advance of the influenza season) as two antigenically distinct lineages (B/Victoria/2/87-like and B/Yamagata/16/88-like) have co-circulated in humans since 1985 (for further details on rationale for the drug development see *Clinical rationale* below). Cross-immunity between the 2 lineages is also variable in humans.

The proposed treatment regimen is the same as for Fluarix®, that is, active immunisation of adults and children from 3 years of age with a single 0.5 mL intramuscular (IM) dose, children 3 years to less than 9 years who have not been previously vaccinated against influenza should receive a second 0.5 mL dose after an interval of at least 4 weeks.

The sponsor proposed the following *Dosage and Administration* instructions:

Fluarix Tetra should be administered as a single 0.5 ml injection.

Children 3 years to less than 9 years of age who have not previously been vaccinated against influenza should receive a second dose of 0.5 ml after an interval of at least 4 weeks.

Vaccination should be carried out by intramuscular injection preferably into the deltoid muscle or anterolateral thigh (depending on the muscle mass).

Regulatory status

This is a new chemical entity for Australian regulatory purposes.

The vaccine was approved by the FDA under the name Fluarix® Quadrivalent in December 2012.

The following table summarises the international regulatory stats of Fluarix Tetra vaccine.

Table 1. International regulatory status

Country	Product name	Submission date	Status	Approved indication
USA	Fluarix Quadrivalent	14 Feb. 2012	Approved on 14 Dec. 2012	FLUARIX QUADRIVALENT is a vaccine indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. FLUARIX QUADRIVALENT is approved for use in persons 3 years of age and older.
Germany	Influsplit Tetra	29 Feb. 2012	Decentralised Procedure closed on 19 Feb. 2013 German license obtained on 25 Feb. 2013	Fluarix Tetra is indicated for active immunisation of adults and children from 3 years of age for the prevention of influenza disease caused by the two influenza A virus subtypes and the two influenza B virus types contained in the vaccine.
United Kingdom	Fluarix Tetra	02 March 2012	Decentralised Procedure closed on 19 Feb. 2013 UK license obtained on 21 March 2013	
France	Fluarix Tetra	29 Feb. 2012	Decentralised Procedure closed on 19 Feb. 2013 French license obtained on 19 June 2013	

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

The drug substance is the monovalent pooled harvest (MPH) from each of the four influenza strains.

The active substance is composed of inactivated, split virus antigen from Influenza A (H1N1 and H3N2) and Influenza B (Yamagata/16/88 and Victoria/2/87 lineages). All strains are produced according to the same manufacturing process as the licensed trivalent inactivated influenza vaccine (TIV) Fluarix.

Manufacturing process consistency was addressed in terms of working seed stability, isopycnic flow through ultracentrifuge splitting, inactivation and yield for the 4 vaccine strains. The evaluator stated that all;

- manufacturing, container, stability and labelling issues have been resolved.
- viral/prion safety issues have been addressed.
- sterility and endotoxin issues have been resolved.

The specifications for the drug are in-line with the European Pharmacopeia (EP) monograph for Influenza Vaccine (split virion inactivated). The specification for residual

sodium deoxycholate for the H1 and B strain was increased from ≤ 100 to ≤ 160 $\mu\text{g}/\text{mL}$ due to the change in dilution factors required for the QIV.

Appropriate validation data have been submitted in support of the test procedures.

Strain specific stability studies have been undertaken or are in progress for monovalent bulk storage.

Drug product

The composition of Fluarix tetra final container is based on the Fluarix dose and volume. The formulation process for the final bulk involves blending the active ingredients with excipients and adjustment to target concentration with buffer in a stainless steel formulation tank. The vaccine is formulated with a diluent to contain a minimum of 15 μg of Ha per strain, 60 μg per dose. An overage is applied to each strain to ensure compliance to shelf life, based on manufacturing experience. The fill volume included an 'overfill' to ensure the nominal volume is delivered.

Specifications for the Final bulk and final container are given below;

The specifications are in line with the EP or represent an increase in-line with what be expected from an additional strain. The total protein and residuals (formaldehyde and ovalbumin) remain the same as the trivalent vaccine.

The detergent specifications have increased due to the additional strain for both Polysorbate 80 and Octoxinol 10 (Triton-X100) from 1000 $\mu\text{g}/\text{mL}$ to 1330 $\mu\text{g}/\text{mL}$ total detergent content. The endotoxin content has decreased to from ≤ 200 to ≤ 10 EU/mL.

Stability data have been generated under real time conditions for the two syringe types. For the 25G 5/8 needle attached syringe a shelf life of 9 months at 2 to 8° C was acceptable. For the PRTC syringe 12 month shelf life at 2 to 8°C was acceptable. The product packaging states *Do Not Freeze* and *Protect from Light*. No other stability data has been supplied for temperatures outside of 2-8°C.

Quality summary and conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

No outstanding quality (Module 3) issues remain. Consistency of production has been demonstrated over two manufacturing buildings. This is the first quadravalent Influenza vaccine to be registered in Australia. The vaccine contains approximately 30% more detergent than the TIV, 15 μg more haemagglutinin (HA) antigen and an increase in neuraminidase (NA) antigen. Residual amounts of formaldehyde and ovalbumin remain the same as the TIV. At the upper level of specifications for detergent concentration the single radial diffusion (SRD) potency assay was found not to conform. The company plans to either revalidated the assay or tighten detergent specifications prior to commencement of commercial production.

The quality evaluator(s) recommend that for Fluarix Tetra 1 x, 10x 15 $\mu\text{g}/\text{dose}/\text{strain}$ HA 25 G 5/8 needle attached and PRTC syringe a shelf life of 9 months and 12 months respectively should be approved.

Batch release conditions of registration for the TGA Delegate (extract)

Conditions of registration: Batch release testing by OLSS

It is a condition of registration that all independent batches of Fluarix Tetra 1 x, 10x 15 µg/dose/strain HA 25 G needle attached and PRTC syringe imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services (OLSS).

For each batch of vaccine imported into Australia the sponsor should supply the following:

- Complete summary protocols for manufacture and QC, including all steps in production.
- Number of doses to be released in Australia from each shipment.
- Evidence of maintenance of satisfactory transport conditions between the manufacturer and Australia, such as graphs of temperature recordings, and a statement that the approved storage conditions have been met.
- At least 20 doses of each first consignment of product lot with the Australian approved labels, PI and packaging. 3 doses of any further consignment of already released product (including diluents) with the Australian approved labels, PI and packaging.
- Certificate of Release from the regulatory agency acting for the country of origin (OMCL).
- Any reagents, reference material and standards required to undertake testing, as requested by OLSS, at least 12 months prior to supply of the vaccine in Australia.

Distribution of each shipment of each batch of vaccine is conditional upon fulfilment of these conditions and receipt of a letter from the Office of Laboratories and Scientific Services (OLSS) allowing release. Arrangement for delivery of the requested items will be provided.

Samples and data should be forwarded to the Immunobiology Section, OLSS before release of each batch and with sufficient lead time to allow for OLSS testing.

These batch release conditions will be reviewed and may be modified on the basis of actual batch quality and consistency.

Certified product details

An electronic draft of the Certified Product Details (CPD), as described in Appendix 7 of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM)², should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when any changes to finished product specifications and test methods are approved.

III. Nonclinical findings

Introduction

The sponsor submitted 2 acute and 2 repeat-dose toxicity studies as well as 2 reproductive and developmental toxicity studies. All studies were Good Laboratory Practice (GLP) compliant. One of the repeat-dose and one of the reproductive and developmental toxicity studies have been evaluated by the TGA previously. The toxicity

² Guidance 7: Certified product details <<http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm>>

studies tested investigational AS03³-adjuvanted trivalent (TIV) and quadrivalent influenza vaccines (QIV) containing antigens manufactured by the Fluarix[®] process. The previously evaluated reproductive and developmental toxicity study was performed with the related TIVs Fluarix[®] and FluLaval[®] vaccines whereas the new study was conducted with the QIV.

Pharmacology

Primary pharmacology

No nonclinical protective efficacy studies were submitted. In contrast to influenza A viruses, the host range of influenza B viruses is limited primarily to humans. Influenza B viruses may replicate in the respiratory tract of mice but generally require prior adaptation to cause disease and mortality. Influenza B virus may infect ferrets and cause similar disease to humans, without adaptation, however pathogenesis has been reported to be milder and lung viral titers lower with influenza B than with influenza A virus⁴. In mice and ferrets the antibody response to inactivated influenza vaccine may be low without prior priming by exposure to influenza virus antigens⁵.

The sponsor provided immunogenicity data in C57B1/C6 strain of mice and ferrets from studies conducted for the purpose of developing seasonal TIV and QIV adjuvanted with AS03, in which the corresponding unadjuvanted vaccines were used as references. In C57Bl/6 mice a single dose of unadjuvanted TIV or QIV induced low haemagglutinin inhibitory (HI) titers (<40) against B/Shandong/7/97 (Victoria lineage) and negligible HI titers against B/Jiangsu/10/2003 (B-Yamagata-like), even when the mice had been primed with a B/Yamagata-like virus. In ferrets vaccinated on Days 0 and 21 with unadjuvanted TIV or QIV, HI titers against B/Brisbane/03/2007 were negligible after the first dose and low after the second dose, and were substantially boosted by lethal intratracheal challenge with the homologous vaccine B strain. The sponsor concluded that the animal models were not suitable to test the immunogenicity of the unadjuvanted QIV. Nonetheless, the QIV induced high levels of seroconversion in rats and rabbits, the toxicology test species.

In the absence of nonclinical protective efficacy studies and inconclusive animal immunogenicity data, the demonstration of efficacy and immunogenicity will depend on clinical data. The sponsor claimed that clinical studies showed that the additional B strain had superior immunogenicity to Fluarix[®] and did not diminish the immunogenicity of the 3 original strains in adults and children from the age of 3 years (sponsor's *Nonclinical Overview*).

Pharmacokinetics

No new studies submitted.

³ GSK's adjuvant (Oil-in-water emulsion)

⁴ Kim YH et al (2009). Influenza B virus causes milder pathogenesis and weaker inflammatory responses in ferrets than influenza A virus. *Viral Immunology* 22 (6): 423-430.

⁵ Potter CW and Jennings R (2003). Effect of priming on subsequent response to inactivated influenza vaccine. *Vaccine* 21: 940-945.

Toxicology

Acute toxicity/local tolerance

The addition of a fourth antigen to the QIV raises the HA antigen from 45 to 60 µg total, the proposed specification for total protein in the final bulk is 600 µg/mL. The specified levels of the excipients α -tocopherol hydrogen succinate, octoxinol 10 and polysorbate 80 are about one third higher in the QIV compared to Fluarix[®], in order to maintain the same ratios to HA as in Fluarix[®].

Two acute toxicity/local tolerance studies in rabbits were submitted; the first used an investigational QIV adjuvanted with AS03 containing 60 µg HA produced with the Fluarix[®] process. Clinical observation and macroscopic examination at necropsy did not reveal any local reactions, microscopy of injection sites on Day 3 revealed a very slight to slight, widespread mononuclear cell type of inflammatory response. The second study, which used an investigational TIV adjuvanted with AS03 containing 45 µg HA per dose and Fluarix[®] as a reference vaccine showed injection site reactions in the Fluarix[®] group were microscopically comparable with saline controls. Injection site reactions with the adjuvanted vaccine were more pronounced and were attributable to the adjuvant.

Repeat-dose toxicity

Two repeat-dose toxicity studies in rabbits were submitted; the first used the QIV adjuvanted with AS03 containing 60 µg HA ("Flu NG QIV60/AS03B"), a previously evaluated study with the TIV adjuvanted with AS03 used Fluarix[®] as a reference vaccine. In the new study rabbits were injected on Days 0, 14 and 18, and sacrificed on Day 31 or 55. Clinical observation and macroscopic examination did not reveal any local reactions. Rectal temperatures showed no toxicologically significant effects. Haematology and clinical chemistry showed transient increases in fibrinogen and white blood cell counts (WBCs), mainly involving neutrophils and eosinophils, and decreased albumin/globulin ratios after the first and third doses. These changes being characteristic of the inflammatory response to the adjuvant and injection process and the immune response. Microscopic examinations of the injection sites showed very slight to slight widespread inflammation of a mixed cell type in the treated group, which had resolved to very slight multifocal inflammation at Day 27 after the third dose. Activation of the draining lymph nodes and spleen were a consequence of the immune response. There was 100% seroconversion in this study. Similar observations were made in the previously evaluated study in which rabbits were injected on Days 1 and 24 with the AS03-adjuvanted TIV and Fluarix[®] was used as a reference vaccine. Microscopy of injection sites on Day 27 in Fluarix[®] treated rabbits showed similar reactions to saline controls. Perivascular cuffing, fasciitis and lymphoid hyperplasia were less severe than with the adjuvanted vaccine and had resolved in almost all rabbits by Day 52. All rabbits seroconverted in this study.

In conclusion, the toxicity studies do not raise any concerns and the local tolerance⁶ was considered to be acceptable.

Dose multiples in toxicity studies

The table below shows that adequate multiples of the human dose (on a mg/kg basis for both adults and children) were tested in all the toxicity studies.

⁶ See *Local tolerance* below for details of the studies conducted.

Table 2. Animal/ human dose multiples

Study (no.) (year)	Test vaccine dose (IM)	HA dose	Animal/human dose multiple*
Rabbit acute toxicity (TNO 8412) (2010)	Single human dose (0.7 mL) QIV/ASO3	60 µg	20x (adult) 6x (3 y.o. child)
Rabbit acute toxicity (Covance 1620/009) (2004)	Single human dose (0.5 mL) of (i) Fluarix® (left thigh)+ ASO3 (right thigh) or (ii) TIV 15 µg/ASO3 (left thigh), TIV 7.5 µg/ASO3 (right thigh)	(i) 45 µg (ii) 45/22.5 µg	15x (adult) 4x (3. y.o. child)
Rabbit repeat-dose toxicity (Covance 1620/008) (2004). Previously evaluated for PrePandemrix®	Human dose (0.5 mL) of (i) Fluarix® or (ii) TIV/ASO3 on Days 1, 24	45 µg	15x (adult) 4x (3. y.o. child)
Rabbit repeat-dose toxicity (TNO 8493) (2010)	Human dose (0.7 mL) of QIV on Days 0, 14 and 28.	60 µg	20x (adult) 6x (3. y.o. child)
Rat reproductive toxicity (HLS GVB009/06374) (2007). Previously evaluated for Arepanrix® H1N1	1/5 th human dose (0.1 mL) of Fluarix® or FluLaval® on Days -28, GD 6, 8, 11 and 15.	9 µg	30x (adult)
Rat reproductive toxicity (HLS HEY 007) (2011)	2/5 th human dose (0.2 mL) of D-QIV, Q-QIV on days -28, -14, GD 3, 8, 11, 15, LD 7.	24 µg	80x (adult)
HA = haemagglutinin, TIV = trivalent influenza vaccine, QIV = quadrivalent influenza vaccine. D=Dresden, Q= Quebec. Y.o.=year old, ASO3 is an oil-in-water emulsion adjuvant containing squalene, α-tocopherol, and polysorbate 80, GD=gestational day, LD=lactation day. *Based on bodyweights of 2.5 kg (rabbit), 250 g (rat), 50 kg (adult human), 13.8 kg (3 year old female child 50 th percentile, US Centers for Disease Control clinical growth charts).			

Reproductive toxicity

Influenza vaccination is recommended for pregnant women⁷. The sponsor submitted two reproductive and developmental toxicity studies, conducted in accordance with the

⁷ Australian Government Department of Health and Ageing. The Australian Immunisation Handbook, 10th edition, 2013.

relevant nonclinical guidelines⁸ consisting of a previously evaluated study of Fluarix® and FluLaval® in rats and a new study with the QIV. In the new study, female rats administered the QIV twice prior to mating and on GD 3, 8, 11 and 15 and LD 7 showed no effects on fertility, pregnancy, parturition, lactation or embryofetal or pre-weaning development. Vaccine antigen-specific antibodies were transferred from the rat dams to the fetuses and lactating pups. The previous study showed no effects on female rat fertility and embryofetal development with either TIV.

An Australian Pregnancy Category of B2⁹ was proposed for Fluarix® tetra. In light of the negative findings in the reproductive and developmental toxicity study with the QIV, a category of B1¹⁰ is acceptable. The sponsor has a postmarketing commitment with the USA FDA to establish a pregnancy registry for Fluarix® Quadrivalent for USA vaccinees, with annual reports submitted in the periodic safety update reports and a full 5 year report.

Local tolerance

Local tolerance was investigated by injection site observations, modified Draize scores and macroscopic and microscopic examination of injection sites in all of the acute and repeat-dose toxicity studies (see *Toxicity* above).

Paediatric use

Fluarix® tetra is proposed for use in children from the age of 3 years. No nonclinical toxicity studies were conducted in infant animals, however, rat fetuses and lactating pups were exposed to vaccine antigen-specific antibodies in the reproductive toxicity studies without adverse effects. Furthermore, the HA doses in the acute and repeat-dose toxicity studies were adequate multiples of the human dose, adjusted for a 3 year old human female bodyweight (see Dose Multiple Table 2 above).

Residuals/impurities

The QIV may contain formaldehyde, ovalbumin, sodium deoxycholate, gentamicin and hydrocortisone as residuals/impurities. Although their levels may be increased in relation to the TIV, toxicity at the proposed specifications is unlikely. The residuals are listed in the product information.

Nonclinical summary and conclusions

1. No nonclinical protective efficacy studies were submitted and immunogenicity data in mice and ferrets were inconclusive. The demonstration of vaccine efficacy/immunogenicity will depend on clinical data.

⁸ CPMP Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines (CPMP/SWP/465/95).

World Health Organization WHO Technical Report Series, no. 927, 2005. Annex 1. WHO Guidelines on nonclinical evaluation of vaccines.

FDA Guidance for Industry. Considerations for developmental toxicity studies for preventive and therapeutic vaccines for infectious disease indications. CBER February 2006.

⁹ **Category B2:** Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

¹⁰ **Category B1:** Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

2. Acute/local tolerance and repeat-dose toxicity studies in rabbits administered the human dose of the QIV or related TIVs did not reveal any vaccine-related toxicity and local inflammation at injection sites was minor and transient.
3. Reproductive and developmental toxicity studies in female rats administered 1 or 2 fifths of the human dose of the QIV or related TIVs showed no effects on female fertility, pregnancy, parturition, lactation and embryofetal and pre-weaning development. Almost all dams seroconverted and vaccine antigen-specific antibodies were detected in their fetuses and pups. Adequate multiples of the human dose was administered to both rabbits and rats, on a mg/kg basis for both adults and children.

Recommendations

No nonclinical protective efficacy studies were submitted for Fluarix® tetra and immunogenicity data in mice and ferrets were inconclusive. The demonstration of vaccine efficacy and immunogenicity will depend on clinical data.

Acute and repeat-dose toxicity studies in rabbits with the QIV and related TIVs did not reveal any vaccine-related toxicity and local inflammation at injection sites was minor and transient. Reproductive and developmental toxicity studies in rats with the QIV and related TIVs revealed no vaccine-related toxicity. An Australian Pregnancy Category of B1 is recommended. Adequate multiples of the human dose, on a mg/kg basis for both adults and children, were administered in all toxicity studies. There are no nonclinical objections to registration, provided that the clinical data demonstrate satisfactory vaccine efficacy/immunogenicity.

The nonclinical evaluator recommended amendments to the draft Product Information but the details of these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

The evaluator's summaries of the clinical findings are included under *First Round Summary and Discussion* below.

Clinical rationale

GlaxoSmithKline's (GSK's) development of the quadrivalent vaccine is based on their rationale as follows:

Influenza B causes outbreaks every 2 to 4 years, which are accountable for a substantial number of hospitalisations and deaths. Surveillance in the United States since 1976 showed that the overall rate of infection due to influenza B was greater than due to Influenza A subcategory H1N1 (A/H1N1), and that influenza B was second in rank after influenza A subcategory H3N2 (A/H3N2) in terms of lethality.¹¹ From 1990 to 1999, 16% of the influenza-associated deaths in the overall population in the US (8,349) were due to influenza B. Eighty-six percent of these influenza B deaths occurred in individuals ≥65 years of age, where they represent 16% of all

¹¹ Thompson WW, Shay DK, Weintraub Et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 2003;289:179-186

influenza-related deaths. Although influenza B mortality is prominent in the elderly, paediatric deaths due to influenza B also occur and account for 46% of all influenza-related deaths in children below the age of 5 years.¹¹

From the late 1970's, influenza B viruses have diverged into two genetically distinct phylogenetic lineages on the basis of their haemagglutinin. Since the mid 1980's the two lineages represented by the B/Victoria/2/87 and B/Yamagata/16/88 strains have been co-circulating in varying proportions in different years and countries^{11,12,13} As only a single B strain is included in the currently licensed trivalent seasonal influenza vaccines, each season there is a risk of disparity between the strain recommended for inclusion in the trivalent influenza vaccines and the dominant circulating B strain, which may vary geographically. High rates of influenza B mismatch have been reported in studies conducted in different regions and countries worldwide as summarised in Table 3.

The available evidence supports some cross-reactivity between the two B lineages, with variable levels across studies. However trivalent influenza vaccine efficacy against influenza B due to the non-vaccine lineage is less than against influenza B due to the vaccine lineage or vaccine-matched influenza A strains. In unprimed children, there is evidence of low or almost non-existing cross-reactivity of antibodies between the two B lineages.^{14,15}

Table 3. Examples of high Influenza B lineage mismatches in recent years

Country	Year	Vaccine B lineage	Main circulating B lineage (% of all circulating influenza B = % mismatch)
Philippines & Thailand (Chi, 2005)	2002	Yamagata	Victoria (96%)
Taiwan (Jian, 2008)	2003-04	Victoria	Yamagata (100%)
Australia (Turner, 2005)	2004	Victoria	Yamagata (100%)
Taiwan (Jian, 2008)	2004-05	Yamagata	Victoria (64%)
Italy (D'Agaro, 2008)	2004-05	Yamagata	Victoria (83%)
New Zealand (Huang, 2007)	2005	Yamagata	Victoria (82%)
Myanmar (Dapat, 2009)	2005	Yamagata	Victoria (85%)
Europe (Meijer, 2007)	2005-06	Yamagata	Victoria (90%)
Czech Republic (Beran, 2009)	2005-06	Yamagata	Victoria (92%)
Hong Kong (Chiu, 2009)	2005-06	Yamagata	Victoria (100%)
Australia (Miller, 2008)	2007	Victoria	Yamagata (76%)

Contents of the clinical dossier

Five studies were presented in support of the application:

Two pivotal, Phase III studies, Studies D-QIV-008 and D-QIV-003, evaluated the candidate D-QIV vaccine in adults from 18 years of age and children from 3 years of age respectively. Both studies included two comparator groups, one receiving the seasonal trivalent influenza vaccine Fluarix, the other a similar trivalent vaccine containing a strain of the B lineage not included in the seasonal vaccine.

Two supportive studies, Studies D-QIV-001 (Phase I/II) and D-QIV-002 (Phase II), evaluated the candidate vaccine in adults from 18 years and children from 18 months of age. These studies included a control group that received the seasonally recommended trivalent influenza vaccine.

¹² Shaw MW, Xu X, Li Y et al. Reappearance and global spread of variants of Influenza B/Victoria/2/87 lineage viruses in the 2000-2001 and 2001-2002 seasons. *Virology* 2002;303:1-8;

¹³ Belshe RB. The need for quadrivalent vaccine against seasonal influenza. *Vaccine*. 2010 Sep 7;28 Suppl 4:D45-53

¹⁴ Levandowski RA, Regnery HL, Staton E, Burgess GB, Michael S, Williams MS, Groothuis JR. Antibody Responses to Influenza B Viruses in immunologically unprimed children. *Pediatrics* 1991; 88 (5): 1031-6.

¹⁵ Englund JA, Walter EB., Gbadebo A., Monto AS., Zhu Y, Neuzil KM. Immunization with trivalent inactivated influenza vaccine in partially immunized toddlers. *Pediatrics*. 2006;118:579-585.

A further study, Fluarix-US-006 (Phase IV) evaluated the efficacy, safety and immunogenicity of Fluarix trivalent vaccine versus placebo control in an adult population.

Paediatric data

Paediatric data were submitted with Studies D-QIV-003 and D-QIV-002.

Good clinical practice (GCP)

GSK asserts that all studies were conducted in accordance with GSK standard operating procedures, which comply with the principles of Good Clinical Practice (GCP), the Declaration of Helsinki, the US Code of Federal Regulations and local rules and regulations. The studies were conducted with the approval of an Ethics Committee or Institutional Review Board. Written informed consent was obtained from all participants, or parents or legal guardians, prior to the performance of any study-specific procedures.

The study designs took into account the FDA “*Guidance for Industry Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines*” (CBER, 2007).¹⁶; and the European Union (EU) “*Guideline on Clinical Evaluation of New Vaccines*” (EMA/CHMP/VWP/164653/2005; EMA, 2006).¹⁷, “*Guideline on Similar Biological Medicinal Products*” (CHMP/437/04; CHMP, 2005).¹⁸ and “*Note for Guidance on Harmonization of Requirements for Influenza Vaccines*” (CPMP/BWP/214/96; CPMP, 2005).¹⁹. All central and local clinical trial activities were governed by the International Conference on Harmonization, Good Clinical Practice guidelines. All members of staff working on clinical trials were appropriately qualified and trained in GCP and GSK procedures.

Pharmacokinetics

Not applicable.

Pharmacodynamics

Not applicable.

Efficacy

Immunogenicity was assessed by measurement of haemagglutination inhibiting (HI) antibodies using the method described by the WHO Collaborating Centre for influenza, Centers for Disease Control, Atlanta, USA (1991).

In all studies, “D-QIV” referred to the candidate quadrivalent vaccine, TIV-1 referred to the registered trivalent vaccine, Fluarix, which contained one of the strains included in the quadrivalent vaccine. TIV-2 referred to a trivalent vaccine with a B strain lineage differing from that of the registered trivalent vaccine but contained in the quadrivalent vaccine.

¹⁶ Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines
<<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074794.htm>>

¹⁷ EMA/CHMP/VWP/164653/2005 Guideline on clinical evaluation of new vaccines

¹⁸ CHMP/437/04 Guideline on similar biological medicinal products

¹⁹ CPMP/BWP/214/96 Note for guidance on harmonisation of requirements for influenza vaccines
<http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003945.pdf>

Guidelines for licensure of trivalent vaccines

Levels of HI antibody titres post vaccination have not been correlated with protection from influenza illness but have been used as a measure of vaccine activity. The immunological criteria defined in the *Note for Guidance on Harmonization of Requirements for Influenza Vaccines* (CPMP/BWP/214/96; CPMP, 2005)¹⁹ are applicable to adults. In the absence of specific criteria for children, data were assessed using the existing criteria for 18 to 60 year old adults. These guidelines, which have been adopted in Australia, were summarised in a table.²⁰

Safety

Patient exposure

In total, 4,228 individuals were exposed to at least one dose of D-QIV vaccine in Phase III studies: 3,036 adults 18 years of age and older and 1,192 children from 6 months to 17 years of age; 915 of whom were in the 3 to 17 years age group. In the paediatric studies, safety data are available from 534 children who received one dose and 956 children who received two doses. In addition safety data from 298 children and 105 adults from the two supportive studies contributed to the total safety database.

Adult participants ranged in age from 18 to 92 years in Study D-QIV-008 and 18 to 59 years in Study D-QIV-001. The study populations were of predominantly White Caucasian/European heritage (71%), followed by East Asian heritage (24%).

Paediatric participants enrolled in supportive Study D-QIV-002 range in age from 18 to 47 months. In pivotal Study D-QIV-003, the age range of individuals enrolled was 6 months to 17 years. In each study, the demographic characteristics were similar for the D-QIV and comparator groups.

The primary analysis of safety and reactogenicity was performed on the Total Vaccinated Cohort including all individuals with at least one vaccine administration documented.

²⁰ Summary of CPMP/BWP/214/96 Harmonisation of Requirements for Influenza Vaccines

The tolerance and efficacy of the vaccine shall be evaluated separately in two groups of at least 50 healthy volunteers, aged between 18 - 60, and over 60 years of age. For the latter group it is important that the prior vaccination status be known.

At least one of the assessments should meet these requirements.

Sera should be assayed for anti-HA antibody against prototype strains by haemagglutinin inhibition or single radial haemolysis tests. A (HI) titre is considered protective if ≥ 40 .

Seroconversion is defined in terms of HI. For individuals with a pre-vaccination titre < 10 (1/dil), a post-vaccination titre ≥ 40 (1/dil) represents seroconversion

For individuals with a pre-vaccination titre ≥ 10 (1/dil) a ≥ 4 fold increase from pre to post-vaccination titre represents a significant rise in antibody titre.

Guideline requirements for adults 18 - 60 years

1. The rate of seroconversions or significant increase in anti-HI antibody titre should be $> 40\%$
2. Mean geometric increase between day 0 and Day 21: > 2.5
3. The proportion of individuals achieving an HI titre ≥ 40 should be $> 70\%$.

Requirements for adults over 60 years

1. The rate of seroconversion or significant increase in anti-HI antibody titre: $> 30\%$
2. Mean geometric increase between day 0 and day 21 should be > 2
3. The proportion of individuals achieving an HI titre ≥ 40 or SRH titre $\geq 25\text{mm}^2$ should be $> 60\%$.

First round summary and discussion

In support of the application, one pivotal adult and one pivotal paediatric study were submitted, along with 2 supporting adult studies and one supporting paediatric study.

The **pivotal adult study FLU- D-QIV-008** was conducted in Germany, Romania, Spain, Korea, Taiwan and the US between October 2010 and June 2011. It was a Phase III, partially-blind, controlled, parallel group study to evaluate immunogenicity, safety and reactogenicity of D-QIV vaccine in adults 18 years of age and over, who were either healthy or had chronic well-controlled disease.

Participants were randomised into 5 groups, 5:5:5:5:3. Three groups of 1012 were vaccinated with three different lots of the candidate D-QIV vaccine; 1010 participants were vaccinated with Fluarix including the B/Victoria and 610 with TIV-2 vaccine which was identical to Fluarix except for inclusion of the B/Yamagata. Demographics were evenly spread. Participants ranged in age from 18 to 92 years. Over two thirds were White Caucasian and approximately a quarter was East Asian. Withdrawal rate was less than 2%.

Co-primary objectives were to assess:

- Lot-to lot consistency of HI antibody GMTs of three lots of the quadrivalent influenza vaccine D-QIV.
- Non-inferiority in terms of HI antibody GMTs and seroconversion rates of D-QIV compared to trivalent influenza vaccine TIV-1 (Brisbane) and TIV-2 (Yamagata) vaccine for the three strains that were included in each of the two trivalent vaccines.
- Superiority in terms of GMTs and SCRs of the D-QIV vaccine compared to the two trivalent vaccines for the B strain that was not included in each vaccine.

Lot-to-lot constancy was shown for all three lots. Non-inferiority criteria for HI antibody GMTs and seroconversion rates were met for all vaccine strains shared with the trivalent vaccines. Criteria for superiority of D-QIV to TIVs for the B-strains not included in the trivalent vaccines were met.

Secondary objectives were to describe the immunogenicity in terms of GMTs and seroprotection rate at Days 0 and 21, seroconversion rate and mean geometric increase at Day 21 and to assess reactogenicity and safety.

Baseline seropositivity rates were similar across vaccination groups. The lowest seropositivity rate was for the H1N1 component of the vaccine (53.7% to 58.2%). For H3N2, the rates were approximately 80%, for B virus Victoria lineage rates were approximately 85% and for the Yamagata lineage approximately 86%. For each strain and each vaccine, seroconversion rates, seroprotection rates and fold increases met the CPMP/BWP/214/96 *Harmonisation of Requirements for Influenza Vaccines*¹⁹ guidelines for adults 18 to 60 years of age.

Evaluator comment: This study was well designed and reported and the immunogenicity results generally support the opinion that the quadrivalent vaccine is sufficiently immunogenic to recommend registration for use in adults from 18 years of age. The 2 issues requiring clarification (see *List of Questions* below) were considered to have been satisfactorily addressed in the sponsor's response to TGA's consolidated request for information.

The **supportive adult study FLU-D-QIV-001** conducted in one centre in the Czech Republic between July 2008 and January 2009 was a Phase I/II dose finding single blind, controlled study in adults to evaluate the immunogenicity, safety and reactogenicity of the quadrivalent influenza candidate vaccine.

Participants aged 19 to 59 years were randomised 1:1:1:1 to four groups of 105 participants. The groups were vaccinated with D-QIV or Fluarix or with a low dose

adjuvanted quadrivalent or trivalent vaccine. The quadrivalent vaccine included B/Malaysia/2506/2004 and B/Jiangsu/10/2003. The seasonal vaccine included the B/Malaysia strain. Participants were almost exclusively White Caucasian. Only one participant withdrew from the study and two were excluded from the ATP analyses.

Co-primary objectives relevant to the appraisal of D-QIV were assessment of non-inferiority of HI GMTs of D-QIV versus Fluarix for the three seasonal strains, and superiority of HI GMT of D-QIV versus Fluarix for the B/Jiangsu/10/2003 strain not included in Fluarix. Criteria for non-inferiority were met for the three strains included in the seasonal trivalent vaccine. Superiority in protocol defined terms was shown for strain not included in Fluarix.

Secondary objectives included assessment of humeral immune responses. Baseline seropositivity rates were similar for all vaccine groups and were relatively high: approximately 60% for A/Solomon/H1N1, approximately 80% for A/Wisconsin/H3N2, between 75% 82% for D-QIV and TIV respectively for B/Malaysia and approximately 70% for B/Jiangsu. For D-QIV, seroconversion rates, seroprotection rates and fold increases met Committee for Proprietary Medicinal Products (CPMP) guidelines for adults 18 to 60 years. The guidelines were met for Fluarix for the three antigens included.

Evaluator comment: The study was well conducted and reported. The results support the opinion that the quadrivalent vaccine is sufficiently immunogenic to recommend registration for the age group included in the study. The GMT results did not suggest interference.

Adult efficacy

The **supportive adult efficacy study Fluarix-US-006** was conducted during the influenza season 2006/2007 at one centre in the Czech Republic and fourteen centres in Finland. It was a Phase IV, placebo controlled double-blind trial including healthy adults aged 18 to 64 years. A total of 7652 participants were randomised 1:1:1 to receive Fluarix lot 1, Fluarix lot 2 or placebo (normal saline). The study population was almost exclusively White Caucasian and 60% were female. The withdrawal rate was less than 3%.

The primary objective was to demonstrate efficacy of Fluarix in the prevention of culture confirmed influenza A and/or B cases for vaccine antigenically matched strains compared to the placebo group. The primary objective was met if the lower limit of the 95% confidence interval for the vaccine efficacy against culture-confirmed influenza A and/or B, for vaccine antigenically matched strains, was above 35%.

Active surveillance for influenza like illness was conducted by the investigator approximately bi-weekly during the study period starting from 2 weeks after vaccination until the end of the influenza season. There was a 14 day follow-up period for each influenza like illness (ILI) episode. Influenza like illness was defined as at least one systemic symptom, fever (oral temp $\geq 37.8^{\circ}\text{C}$) and/or myalgia and at least one respiratory symptom.

The first day of an ILI episode was defined as the first day with one systemic symptom and one respiratory symptom. The last day of an ILI episode was defined as the last day either with fever, myalgia, cough or sore throat. A new ILI episode was only to be taken into account after the complete resolution of the previous one. Between two ILI episodes, there had to be at least 7 days free of any symptoms. A swab of both nares and a throat swab were collected at the onset of the ILI for influenza virus culture and identification, classification of influenza A and/or B virus isolates as “vaccine matching” or not, by serological typing and testing for influenza A and/or B by RT-PCR. A diagnosis of pneumonia was confirmed by chest X-ray.

The study found that the lower attack rate in the Fluarix group resulted in vaccine efficacy estimate of 66.9%. The primary objective was met; the lower limit of the confidence interval for the vaccine efficacy (51.9%) was above 35%.

Evaluator comment: Results of this study supports efficacy of vaccination with Fluarix. There were a number of participants who were not swabbed in the protocol defined 5 day interval or who were not swabbed or had swabs lost. In addition, it is unclear how long after the onset of symptoms or influenza infection that swabs were likely to be remain positive. Questions relating to these comments were addressed by the sponsor and the sponsor's responses were accepted.

Adult safety

A total of 3,036 adults were exposed to at least one dose of D-QIV vaccine in Study D-QIV-008 and 105 adults in Study D-QIV-001. No new or unexpected safety signal was detected. In general, in the pivotal study, safety in the D-QIV vaccinated groups mirrored that of the TIV vaccinated groups.

The incidences of solicited AEs were generally similar following vaccination with D-QIV and Fluarix except for injection site pain in supportive Study D-QIV-001, where pain was more common in the D-QIV group (72.4%) than in the Fluarix group (49.5%). In Study D-QIV-008, pain at the injection site was reported by a similar percentage of individuals in the D-QIV group (36.4%) and the TIV-1 and TIV-2 groups (36.8% and 31.3% respectively). In Study D-QIV-008, Grade 3 pain was reported in 0.5%-1.2% of individuals across the 3 vaccine groups. Redness and swelling were reported by 1.3% to 2.1% of individuals. The applicant considers that the smaller number of participants in D-QIV-001 may have biased the results for pain. The evaluator notes that Study D-QIV-001 was not double blind.

In both adult studies, fatigue, myalgia and headache were the most common solicited general symptoms. Incidences of fatigue and headache were higher in supportive Study D-QIV-001 than in the large pivotal Study D-QIV-008, particularly so for fatigue. Examining each study separately, the incidences of events were similar for included vaccine groups. For D-QIV-008 results were; myalgia: D QIV 16.4%, TIV-1 19.4% and TIV-2 16.1%; fatigue: D-QIV 15.8%, TIV-1 18.4% and TIV-2 14.8% and headache: D-QIV 15.9%, TIV-1 16.4% and TIV-2 13.2%. For D-QIV-001 results were: myalgia: D-QIV 16.2% TIV 14.3%, fatigue: D-QIV 31.4%, TIV 32.4% and headache: 23.8%, TIV 24.8%. Grade 3 solicited general events were reported by a maximum of 2.9% of participants, the maximum being for headache in the D-QIV group in supportive Study D-QIV-001.

Lower reactogenicity was seen in participants aged ≥ 65 years in Study D-QIV-008 compared with those aged 18 to 64 years.

The most frequently reported unsolicited AEs were nasopharyngitis, cough and oropharyngeal pain in Study D-QIV-008 and pharyngitis and headache in Study D-QIV-001; all reported at incidences lower than 2.0% in each vaccine group. Few unsolicited AEs were considered vaccine-related, the most common being injection site haematoma and oropharyngeal pain in Study D-QIV-008 reported in 0.2-0.5% of individuals. Severe (Grade 3) AEs after D-QIV vaccination were reported by 1.3% of individuals in Study D-QIV-008 and none in D-QIV-001.

There were no deaths, serious adverse events discontinuations or potential immune mediated diseases considered related to study vaccine.

Evaluator comment: The safety and reactogenicity of D-QIV was found to be similar to that of Fluarix and therefore there appears no safety reason not to recommend registration for adults from 18 years of age.

Paediatric immunogenicity

The **pivotal paediatric study FLU-D-QIV-003** was conducted between October 2010 and June 2011 in the Czech Republic, France, Germany, Philippines and the USA. It was a Phase III, randomised, controlled, multi-country, multi-centre study with four parallel groups. A total of 2741 participants aged 3 to 17 years were randomised 1:1:1 to receive D-QIV, TIV-1 (Fluarix, with B/Victoria) or TIV-2 (with B/Yamagata).

Primed participants were vaccinated with one intramuscular injection on Day 0. By protocol definition, primed participants had received at least one dose of an influenza A (H1N1) 2009 monovalent vaccine in the previous season or had laboratory confirmed H1N1 infection *and* had received two doses of seasonal influenza immunization separated by at least one month during last season or had received at least one dose prior to last season.

Two IM injections at Day 0 and Day 28 were given to unprimed participants. By protocol definition, these children had not received any influenza A (H1N1) 2009 monovalent vaccine in the last season or did not have laboratory confirmed H1N1 infection *or* had not previously received any seasonal influenza immunisation in the past or received only one dose of influenza vaccine for the first time in the last influenza season.

Demographics were similar across the three groups. The population included approximately 56% White Caucasians, approximately 26% South East Asians and approximately 13% African Americans. Over 5% were eliminated from the ATP immunogenicity population; therefore, analyses were conducted on the ATP and the TVC populations.

A fourth group, D-QIV-Y, aged 6 to 35 years was also included in the study. Immunogenicity results for this group were not evaluated here; however the group was examined for safety.

The following objectives were based on results from participants 3 to 17 years of age. The primary objective was to evaluate immunological non-inferiority of D-QIV versus TIV-1 containing B/Victoria lineage and TIV-2 containing B/Yamagata lineage, in terms of GMT and SCR 28 days after completion of the vaccination series (Day 28 for primed individuals, Day 56 for unprimed participants). Evaluation of immunological superiority in terms of GMTs and SCR, of D-QIV versus TIV-1 and TIV-2 for the B strain not contained in each TIV formulation was a secondary objective. Other secondary objectives were to describe the immunogenicity in terms of GMTs, seroprotection rate, seroconversion rate and mean geometric increase and to assess reactogenicity, and safety.

The primary objectives were met. Non-inferiority of D-QIV versus Fluarix and TIV-2 and D-QIV versus TIV-2 for the common antigens was demonstrated. Superiority of D-QIV versus the two TIV vaccines was demonstrated for the B strain not included in the TIV vaccines.

Baseline seropositivity rates were between 63.5% and 68.9% for A (H1N1), between 76.1% and 79.4% for A (H3N2), approximately 75% for B (Victoria) and 92% for B (Yamagata). GMTs rose post vaccination for all antigens but more so for antigens contained in the vaccines.

Seroprotection rates post vaccination were high and met the CPMP criteria for adults 18 to 60 years for all antigens included in the vaccines and for B/Brisbane not contained in the TIV-2 vaccine. Seroprotection rate for the B/Yamagata strain not contained in TIV-2 met the criterion for adults over 60 years of age. Mean fold changes met the CPMP criterion for adults 18 to 60 years for all antigens, irrespective of inclusion in a particular vaccine; however, fold rises were considerably higher for antigens included in the vaccines.

Evaluator comment: Results of this well conducted, well reported study support the opinion that immunogenicity is sufficient to recommend registration.

The **supportive paediatric study FLU-D-QIV-002** conducted between October 2009 and May 2010 in two centres in Mexico, was a Phase II, double-blind, multicentre, randomised study evaluating immunogenicity, reactogenicity and safety of D-QIV compared with the Fluarix, in children 18 to 47 months of age.

In all, 599 children were randomised 1:2:1:2 into four groups with approximately 100 children in each of the D-QIV and TIV primed group and 200 in each of the D-QIV and TIV unprimed groups. By study definition, unprimed children had not been vaccinated with 2 doses of influenza vaccine in the previous season and received two doses of vaccine in the study. Primed children had previously received 2 doses of Fluarix 0.5 mL in the GSK Biologicals' Study Fluarix-US-007 the preceding season and were vaccinated with one dose in Study D-QIV-002. The B virus lineage of the priming vaccine could not be determined and thus was inferred from results. The sponsor was asked to provide details of the B strain lineage contained in the priming vaccine and the sponsor's response was accepted by the evaluator (see Question 7 under *List of Questions* below).

The primary objective was to assess non-inferiority of D-QIV for the three recommended seasonal strains. Assessment of superiority of D-QIV compared to TIV for the B strain not included in the trivalent vaccine was a secondary objective. The primary object was met for the three recommended seasonal strains according to the protocol. Superiority was demonstrated for the B strain not included in the TIV vaccine.

Humeral immune response was assessed as a secondary objective. Baseline seropositivity results were higher for the primed participants than for the non-primed, even for the B strain not included in the priming vaccine; however, seropositivity result for the B strain not included in the priming vaccine for both primed and unprimed children was considerably lower than for other strains.

Seroconversion rates for A/H1N1 met the CPMP criterion for adults 18 to 60 years except for primed participants in the D-QIV group which met the criterion for adults over 60 years of age. For A/H3N2 and B/Victoria, the criterion was met for all groups. For B/Yamagata, the result was better for D-QIV but still passed the CPMP criterion for participants in the TIV group who were not vaccinated with the B/Yamagata strain. Fold increases met the CPMP criterion for adults 18 to 60 years for all antigens and were higher in the unprimed than the primed participants.

Seroprotection rates for B/Victoria met the CPMP criterion for adults 18 to 60 years for both unprimed groups but both primed groups failed to reach criteria both for adults 18 to 60 years and over 60 years of age. For the B/Yamagata strain, results met the CPMP criterion for adults 18 to 60 years for all but the TIV unprimed group which met the criterion for adults over 60 years.

Evaluator comment: There are questions to be answered before final conclusions are made; see *List of Questions*. The study design and reporting complicated interpretation of results. Although the children in this study were generally younger than those for whom the indication is proposed, there was a proportion between 36 and 47 months of age, relevant to this application. These children were not separately analysed. The results overall, suggest that a young child previously vaccinated with a trivalent vaccine, may benefit from two doses at first vaccination with the quadrivalent vaccine.

Paediatric safety

In total, 1192 children from 6 months to 17 years of age were exposed to at least one dose of D-QIV vaccine in the Phase III D-QIV-003 study; 915 of whom were in the 3 to 17 years age group. Safety data were available for 534 children who received one dose and 956 children who received two doses of the D-QIV vaccine. An additional 298 children from the supportive Study D-QIV-002 contributed safety information.

The most common solicited local AE was injection site pain reported by approximately 40% to 50% of participants across all studies groups. Grade 3 pain was reported by 0.2% to 2.3%. Redness and swelling were less common and were reported at similar rates across the vaccine groups in both studies. Pain tended to be reported by fewer participants aged 6 to 35 months (30.5%) than in children aged 3 to 17 years, possibly related to developmental language ability, while a trend to more reports of redness (28.4%) was observed in the youngest group.

In children aged 6 to 17 years from Study D-QIV-003, the most frequently reported solicited general symptoms were fatigue, muscle aches and headache, all reported with frequencies ranging from 16.9% to 21.2% across groups.

The incidences of solicited general adverse events were similar across all study groups in pivotal Study D-QIV-003, regardless of severity and causal relationship. For children aged < 6 years (3 to 5 years in D-QIV-003, 18 to 47 months in D-QIV-002), loss of appetite, irritability and drowsiness were reported for 20.3% to 30.7% of the D-QIV vaccinated children in both studies. Fever was recorded for 17.2% and 25.3% of D-QIV participants in Studies D-QIV-003 and D-QIV-002, respectively.

In general, the incidences of all local and general solicited symptoms were similar following vaccination with D-QIV and the trivalent comparators. The incidences of solicited general AEs, including fever, in children aged 6 to 35 months who received D-QIV vaccine in Study D-QIV-003, were within the same range as in children aged 18 to 47 months in Study D-QIV-002 but were generally higher than in children aged 3 to 17 years in D-QIV-003. Grade 3 fever reports followed 3.9% of doses in 6.5% of individuals in the youngest age ranges.

In Study D-QIV-003 for children aged 3 to 17 years, fever (defined as rectal temperature $\geq 38^{\circ}\text{C}$, oral or axillary temperature $\geq 37.5^{\circ}\text{C}$) was reported for 10.8% of individuals in the D-QIV group, compared to 12.3% in the Fluarix group and 9.4% in the TIV-2 group. The incidence of fever $>38^{\circ}\text{C}$ was 4.6% in the D-QIV group, 4.9% in the Fluarix group and 3.5% in the TIV-2 group. Grade 3 fever defined as $> 39^{\circ}\text{C}$ was reported in 1.8% of individuals in the D-QIV group, 1.1% in the Fluarix group and 0.8% in the TIV-2 group.

Febrile convulsions were considered events of specific interest in pivotal Study D-QIV-003. Two cases of febrile convulsion were reported, both from the D-QIV-Y group. Both cases were reported as SAEs, neither was reported within the 2 days post vaccination enhanced surveillance period and neither was considered related to vaccination: In Study D-QIV-002, one case of febrile convulsion was reported in the D-QIV group and was not considered related to vaccination.

In those participants who received two doses, there was no evidence of an increased incidence of solicited AEs following administration of a second dose compared to the first dose. Grade 3 solicited events were reported following $\leq 1.6\%$ of doses across vaccine groups from both studies.

Few unsolicited AEs were considered vaccine-related ($\leq 2.3\%$ after D-QIV vaccination). Severe (Grade 3) unsolicited AEs were reported for D-QIV; in 2.2% of children aged 3 to 17 years, 3.4% of children aged 18 to 47 months and 7.2% of children aged 6 to 35 months. In both paediatric studies no differences between D-QIV and comparators were observed.

No serious adverse event was considered vaccine related. In Study D-QIV-003, 3 individuals discontinued the study because of an unrelated SAE or AE. One individual in the Fluarix group died due to a road traffic accident; one in the D-QIV group was withdrawn due to non-fatal bacterial gastroenteritis; one in the Fluarix group was withdrawn due to non-serious viral pneumonia.

Two potential immune mediated diseases were reported in Study D-QIV-003, one case of non-serious Bell's palsy and one serious case of Type 1 diabetes mellitus were reported. Neither was considered vaccine related.

Evaluator comment: The safety and reactogenicity of D-QIV was found to be similar to that of Fluarix and therefore there appears no safety reason not to recommend registration for children from 3 years of age.

First round risk benefit assessment

The safety of the quadrivalent vaccine studied in the age groups proposed for registration appears similar to that of the registered trivalent vaccines used in the studies.

Immunogenicity of the quadrivalent vaccine has been demonstrated in the populations studied.

Efficacy of the quadrivalent vaccine has not been determined.

First round recommendation regarding authorisation

The risk benefit balance was determined to be on the side of benefit. Registration of the vaccine was recommended.

The applicant's response to comments on the proposed Product Information was accepted with one exception; in the Dosage and Administration section of the amended draft Product Information, the diagrams have been deleted. This is not recommended. The sponsor was asked to please reinstate the diagram.

List of questions

The clinical questions raised by the evaluator are discussed below together with the sponsor's responses and the evaluator's comments on the sponsor's responses.

Second round evaluation of clinical data submitted in response to questions

Question 1 (D-QIV-008): Please provide the lot-to-lot consistency results for all three lots in Study D-QIV-008.

Sponsor's response:

The sponsor submitted the following table (Table 4).

Table 4. Study D-QIV-008: adjusted GMT ratios of HI antibody at Day 21 for the all pairwise comparisons between two lots of D-QIV for the 4 strains contained in the D-QIV vaccine

Strain	D-QIV-1		D-QIV-2		D-QIV-3		Adjusted GMT ratio (D-QIV-1 / D-QIV-2 ^a)			Adjusted GMT ratio (D-QIV-2 / D-QIV-3 ^a)			Adjusted GMT ratio (D-QIV-1 / D-QIV-3 ^a)		
	N	Adjusted GMT	N	Adjusted GMT	N	Adjusted GMT	Value	95% CI LL	95% CI UL	Value	95% CI LL	95% CI UL	Value	95% CI LL	95% CI UL
A/California/7/2009 (H1N1)	600	196.5	599	209.0	602	197.8	0.94	0.80	1.10	1.06	0.90	1.24	0.99	0.85	1.16
A/Victoria/210/2009 (H3N2)	600	306.8	599	330.6	602	308.9	0.93	0.81	1.06	1.07	0.94	1.22	0.99	0.87	1.14
B/Brisbane/60/2008 (Victoria)	600	410.7	599	396.7	602	405.5	1.04	0.93	1.15	0.98	0.88	1.09	1.01	0.91	1.13
B/Brisbane/3/2007 (Yamagata)	600	605.0	599	599.0	602	600.1	1.01	0.90	1.13	1.00	0.89	1.12	1.01	0.90	1.13

D-QIV-1 = Subjects received D-QIV in Lot 1
D-QIV-2 = Subjects received D-QIV in Lot 2
D-QIV-3 = Subjects received D-QIV in Lot 3

Evaluator comment

The response was accepted. All comparisons were between 0.67 and 1.5 for the four strains.

Question 2 (D-QIV-008): Please compare and discuss the GMT, seroconversion, seroprotection and fold increase results for participants aged 18 to 60 versus those > 60 years of age.

In Module 5 Clinical Study Report (CSR) there was no discussion of the results for participants stratified by age. Of particular interest is the comparison between those ≤ 60 years versus those > 60 years.

While for both age categories, the seroconversion rate, seroprotection rate and fold changes were commensurate with those recommended by CPMP for acceptance of seasonal vaccines and confidence intervals were tight, it was noted that the trivalent vaccines each passed the criteria even for the antigen not included.

In addition, in relation to GMTs responses, those of D-QIV were less than for either TIV-1 or TIV-2 for A/California, and A/Victoria, and in both instances, the A antigen GMTs for those > 60 years were considerably less than for those ≤ 60 years and quite a deal less than for the responses to the B antigens, especially for B-Yamagata including for TIV-1. Does this suggest the possibility of a degree of interference with antibody response to the A antigens?

Sponsor's response

Discussion of the results was provided as requested.

Regarding A antigen responses, GMT point estimates in the D-QIV group are each time within the 95%CI limits of the respective GMTs in the TIV groups. Hence, the results do not allow to conclude that the response to the A strains is lower with D-QIV than with TIV and these slight differences in the point estimate do not suggest a possible interference of DQIV on the response to A antigens.

When comparing A antigen responses to those against the B antigens it is observed that GMTs responses to the A antigens are lower than GMTs of antibodies against the B antigens. However, this is mainly due to the particularly high responses to the B antigens in this study, an observation that was made in other studies performed during the same season 2010 to 2011; as further discussed below. Both Yamagata and Victoria B strains had been circulating in preceding influenza seasons and a very high proportion of subjects (approximately 85%) in Study D-QIV-008 were seropositive to the two B strains before vaccination.

Evaluator comment

Response accepted.

Question 3 (Fluarix-US-006): It was noted that the H3N2 the GMTs in Study 008 were higher than in Fluarix-US-006, approximately 310 versus 133. In Study Fluarix-US-006, although the primary objective was met, 77.8% of the 19 cases of influenza A H3 were vaccine matching. Were the GMTs of those with vaccine matching influenza examined?***Sponsor's response***

The absolute figures for GMTs obtained in Study Fluarix –US-006 against H3N2 were indeed lower than those observed in Study D-QIV-008, acknowledging that these were different studies, conducted with different vaccine compositions, in different seasons and in different populations.

As the efficacy results have been mainly driven by the VE against H3N2 in that study, as pointed out by the assessor, this could support the reassuring fact that VE observed in that study represents a worst case situation, leading to lower VE than could be anticipated with higher titres. This has however to be balanced with two elements: on one hand, it can be expected that, depending on the strain, the correlation between HI titres and protection might not be strictly linear. Also, individual immunological responses can vary widely around the calculated GMTs, as evidenced by the maximum (3620) and minimum (>10) HI values observed against H3N2.

Blood samples to assess the immune response were taken from a subset of 460 subjects (6% of total enrolled cohort). Among these, only 3 subjects (all in the placebo group) had culture confirmed influenza due to H3N2, precluding any analysis.

Evaluator comment

Response accepted.

Question 4 (Fluarix-US-006): How long is influenza virus excreted in amounts measurable by the study methods?

Sponsor's response

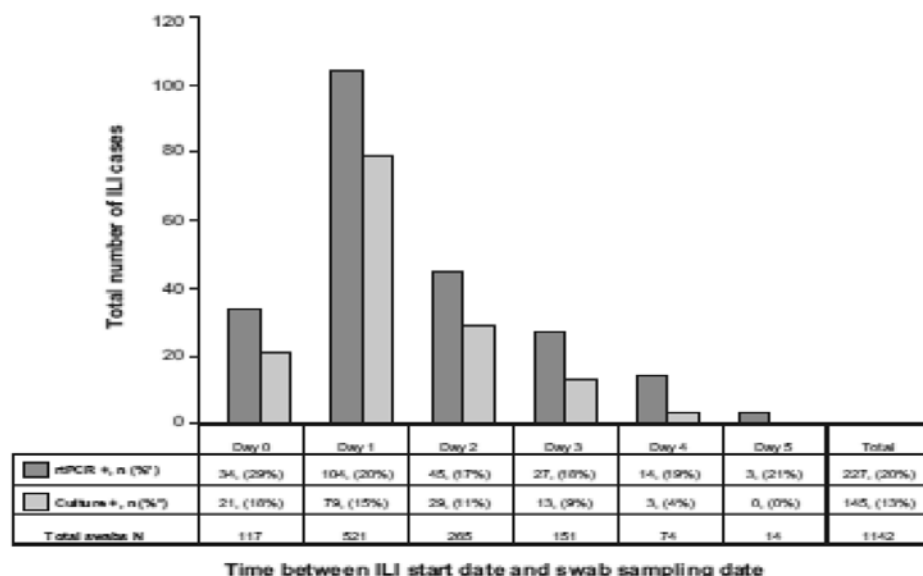
Published data have shown that titres of infectious influenza virus peak during the first 24 to 72 h of illness and decline within several days, with titres usually low or undetectable by Day 5.²¹

In Study Fluarix-US-006, the number of positive samples (by Reverse transcription polymerase chain reaction (RT-PCR) and culture) were stratified per time period between ILI onset and sample (nasal/throat swabs) collection (Figure 1). Among the 1151 ILI cases sampled, 9 were taken after 5 days. Eight were negative by both methods and one was not processed. These 9 cases were not included in the analysis shown in Figure 1 below. For both assays, the maximum percentage of collected swabs that tested positive was recorded on the day of onset of ILI symptoms (that is, Day 0, 29% for RT-PCR and 18% for culture).

Thereafter, the percentage of RT-PCR positive samples remained relatively constant (17 to 21%) while the percentage of culture positive samples decreased progressively from 15% on Day 1 to 0% on Day 5, indicating that RT-PCR was more likely to detect viral shedding later after clinical onset. With both methods, most of the cases were diagnosed on Day 1.

²¹ Bell DM et al; (2006). Non-pharmaceutical interventions for pandemic influenza, international measures. *Emerg Infect Dis* 12:81-7.

Figure 1. Numbers of RT-PCR and culture positive samples stratified by time period between onset of ILI and collection of sample



* % of total swabs positive by rtPCR or culture

ILI: influenza-like-illness

Evaluator comment

Difficulty in diagnosis of influenza illness with increasing length of time between onset and sampling complicates the interpretation of the study results. However, it is acknowledged that this study involved complicated organisation while addressing an important question.

Note: the blurring of Figure 1 is unavoidable due to the blurring of the image in the response document.

Question 5 (Fluarix-US-006): Would the applicant please comment on whether the collection of samples later than 5 days for 7 of the Fluarix group and 2 of the placebo group, had the potential to bias results in favour of Fluarix? In addition, would the applicant specify in which group(s) the swabs were either not taken or were lost?

Sponsor's response

All 9 samples collected later than 5 days in both Fluarix and placebo groups were negative. To check for potential bias, the sponsor tabulated the Vaccine Efficacy as an exploratory analysis, assuming that all the swabs collected after 5 days may have been positive, which represents the worst case for Fluarix efficacy estimates. Table 5 below shows the computations of VE based on the attack rates including the cases taken outside of the 5 day window (assuming all were positive), assuming the event outcome was Binomial distribution. The point estimate for VE is 63% (48.2% to 73.8%), still meeting the criteria for evaluation, that is, LL for 95% CI > 35%.

Table 5. Computations of VE based on the attack rates including the cases taken outside of the 5 day window.

Group	Report			Adding the cases with swabs collected after 5 days		
	N	n	AR	n	AR	VE* (95% CI)
Fluarix	5103	49	1.0	49+7 = 56	1.1	63% (48.2%, 73.8%)
Placebo	2549	74	2.9	74+2 = 76	3.0	

*VE computed using Attack Rates

The number of subjects with samples either not taken or lost is presented per group in the table below.

Table 6. Number of samples not taken or lost.

	Fluarix (N=5103)	Placebo (N=2549)
Swabs not taken or Lost	2	2
Miscase (i.e. visit at home more than 5 days after onset of ILI AND diary card completed)	30	19

Evaluator comment

Response accepted.

Question 6 (D-QIV-003): Study D-QIV-003 Supplement Table 132 (reproduced below as Table 7) had as a footnote “Site 82400 excluded”. Please explain the exclusion of the site.

Table 7. D-QIV-003 Non-inferiority of D-QIV versus TIV-2 in terms of seroconversion rate (difference in seroconversion rate) at Day 28 after the last vaccination for B-Yamagata strain (Total vaccinated cohort)

		TIV-2			D-QIV			Difference in vaccine response rate (TIV-2 minus D-QIV)		
								95% CI		
Antibody	Pre-vaccination status	N	n	%	N	n	%	%	LL	UL
B/Brisbane/3/2007 (Yamagata) (1/DIL)	Total	890	636	71.5	890	655	73.6	-2.13	-6.28	2.01

D-QIV = Subjects of 3-17 years received D-QIV

TIV-2 = Subjects of 3-17 years received TIV-2

Vaccine response defined as :

For initially seronegative subjects : post-vaccination antibody titre \geq 40 1/DIL at POST

For initially seropositive subjects : antibody titre at POST \geq 4 fold the pre-vaccination antibody titre

N = number of subjects with pre- and post-vaccination results available

n/% = number/percentage of subjects with a vaccine response

95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit.

Site 82400 excluded.

Sponsor's response

Supplement Table 132 includes all subjects from all centres: the “site 82400 excluded” note is actually not a footnote but a title applicable to Supplement Table 133. The sponsor apologised for the confusing layout.

In Study D-QIV-003, site 82400 in the US was audited and as quality issues were found, the sponsor decided to also analyse the primary objective of the study excluding the 69 subjects of this site. Though the number of subjects from this centre represented less than 5% (that is, 2.3%) and no difference was expected to be seen, the primary objectives (non-inferiority objectives) were analysed excluding this center for the Total Vaccinated Cohort. Data including and excluding those subjects from the total vaccinated cohort are thus presented in the report:

- The non-inferiority of D-QIV versus TIV-1 (Fluarix) and TIV-2 in children 3 to 17 years old, at 28 days after last vaccination, was presented in Supplement 127 to Supplement 132.
- The non-inferiority of D-QIV versus TIV-1 (Fluarix) and TIV-2 in children 3 to 17 years old, at 28 days after last vaccination excluding the site 82400 was presented in Supplement 133 to Supplement 138.

Excluding site 82400 from the total vaccinated cohort did not affect the outcome of the non-inferiority analysis in the total vaccinated cohort.

Evaluator comment

Response accepted.

Question 7 (D-QIV-002): Please provide details of the B strain lineage contained in the priming vaccine.

Sponsor's response

The sponsor submitted the following table (Table 8).

Table 8. Strain composition of vaccine formulation used in study Fluarix-US- 007

Study/ group	A/H1N1	A/H3N2	B/Victoria	B/Yamagata
Fluarix-US-007				
Fluarix ¹	A/Brisbane/59/2007	A/Uruguay/716/2007	-	B/Brisbane/3/2007
D-QIV-002				
D-QIV	A/Brisbane/59/2007	A/Uruguay/716/2007	B/Brisbane/60/2008	B/Brisbane/3/2007
Fluarix ²	A/Brisbane/59/2007	A/Uruguay/716/2007	B/Brisbane/60/2008	-

1. Recommended CBER/WHO composition: NH season 2008-2009

2. Recommended CBER/WHO composition: NH season 2009-2010

Evaluator comment

Response accepted.

Question 8 (D-QIV-002): Please explain the reason for inclusion of cohorts and sub-cohorts, a design feature which was found difficult to evaluate, particularly when reconciling text with table headings.

Sponsor's response

The reason to create the sub-cohorts was to get only two blood samples in the independent cohort of unprimed children instead of three, that is, the first one on Day 0 and the second one either after Dose 1 or after Dose 2, yet to explore the immune responses after the first and the second dose.

Evaluator comment

The response was accepted. Reporting of cohorts, sub-cohorts and populations for analysis was confusing unlike any other study submitted in this dossier.

Question 9 (D-QIV-002): It appears that there may be some cross reactivity between the 2 B-lineages in primed and unprimed children, or there may have been B-Yamagata circulating in community. Please discuss the findings as the sponsor has previously stated that in unprimed children there is evidence of low or almost non-existing cross-reactivity of antibodies between the two B lineages.

Sponsor's response

The sponsor acknowledged that some level of cross-reactivity is indeed observed between the two B lineages, both in children and in adults. This was observed in Study DQIV- 002 as well as in Studies D-QIV-003 and D-QIV-008.

Results obtained in this suggests that the level of cross-reactivity may increase with age, in line with the hypothesis that cross-reactivity is impacted by previous exposure.

Evaluator comment

Response accepted.

Question 10 (D-QIV-002): SCRs met the CPMP criteria for adults between 18 and 60 years of > 40% for the primed individuals vaccinated with TIV and for both unprimed groups. The result for primed individuals vaccinated with D-QIV met the criterion of > 30% for adults over 60 years. The SCR and SPR results for unprimed participants are considered to suggest that the primed as well as the unprimed, very young children may benefit from a two dose regimen. Please comment.

Sponsor's response

- Dosage was based on that recommended for inactivated influenza vaccines.
- The sponsor acknowledged the somewhat lower immune responses after one dose of vaccine in primed children.
- Primed children had received a vaccine that prevented natural infection whereas unprimed children may have had natural exposure/infection.
- The study was not powered to compare responses of primed versus unprimed children.
- The study population was younger than the lower age limit sought for the Fluarix Tetra indication.
- Responses in primed versus unprimed very young children may vary according to antigens to which they have been exposed.
- A field study would be impossible to validate due to inherent nature of flu vaccines with varying composition each year.

Evaluator comment

The question raised a hypothesis and it was agreed that this could not be tested in D-QIV-002. The hypothesis will become more relevant if the sponsor proposes to register the vaccine for younger children in the future.

Question 11 (D-QIV-003 and D-QIV-002): Regarding the paediatric studies, in reporting of temperature, and in particular in grading of fever, it is unclear whether there was adjustment for method of recording fever. In both studies according to the protocol, fever was defined as: rectal temperature $\geq 38^{\circ}\text{C}$ /axillary temperature $\geq 37.5^{\circ}\text{C}$ /oral temperature $\geq 37.5^{\circ}\text{C}$. The grading shown in the table below does not account for the method of measurement. Was adjustment made for method of measurement in analysis of fever?

Table 9. Studies D-QIV-001, D-QIV-002, D-QIV-003 and D-QIV-008: Intensity scores used for fever

Adults (≥ 18 years) And Children (≥ 6 years of age)			Infants/toddlers and children (< 6 years of age)		
0	:	$< 38.0^{\circ}\text{C}$ (100.4°F)	0	:	$< 38^{\circ}\text{C}$ (100.4°F)
1	:	$38.0 - 38.5^{\circ}\text{C}$ ($100.4 - 101.3^{\circ}\text{F}$)	1	:	$38.0 - 38.5^{\circ}\text{C}$ ($100.4 - 101.3^{\circ}\text{F}$)
2	:	$>38.5 - 38.9^{\circ}\text{C}$ ($>101.3 - 102.2^{\circ}\text{F}$)	2	:	$>38.5 - 39^{\circ}\text{C}$ ($>101.3 - 102.2^{\circ}\text{F}$)
3	:	$\geq 39.0 - 40.0^{\circ}\text{C}$ ($>102.2^{\circ}\text{F}$)	3	:	$> 39.0^{\circ}\text{C}$ ($>102.2^{\circ}\text{F}$)
4 ¹	:	$> 40.0^{\circ}\text{C}$ ($>104^{\circ}\text{F}$)			

1. Grade 4 fever defined in study D-QIV-001 only

Sponsor's response

The sponsor confirmed that for paediatric studies, an adjustment for temperature measurement was done according to the recording route, that is, Grade 1 fever is either $\geq 38^{\circ}\text{C}$ by rectal route or $\geq 37.5^{\circ}\text{C}$ by any other route. Other grades are systematically defined with 0.5°C increment for rectal route.

In the D-QIV 002 study, all temperature measurements (which were recorded and their route known) were done using the axillary route.

In the D-QIV 003 study, approximately 20% of the subjects recorded their temperature using the rectal route while the rest of the subjects measured using the oral, axillary or tympanic route.

Evaluators comment

With respect to D-QIV-002 the response was accepted.

With respect to D-QIV-003, in the absence of confirmation that all measurements were recorded with their route known, it was considered that the potential may have been present to underreport the incidence of fever if correction could not be made when route of measurement was unknown.

Question 12 (All D-QIV studies): Were the disposable needle and syringe used in each of the D-QIV studies the same as that proposed for use with the registered product? If so, were there any accidents reported when the prefilled syringe was being prepared for injection?

Sponsor's response

The presentation used in all D-QIV clinical studies was the plastic rigid tip cap (PRTC), a pre-filled syringe without fixed needle. No incidents or accidents were reported upon the use of this device.

Evaluator comment

The response was accepted.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

The following table shows the sponsor's Summary of the Risk Management Plan for Fluarix Tetra (Table 10).

Table 10. Summary of Risk management Plan for Fluarix Tetra.

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimization activities
<i>Potential risks</i>		
Febrile seizure	<p>Close monitoring of all reports of febrile seizure.</p> <p>Targeted follow-up questionnaire for all reports of febrile seizure.</p> <p>Reports of febrile seizure will be discussed in the PSUR.</p>	<p>No specific risk minimisation is needed at this time. The pharmacovigilance activities described in this RMP/PVP appropriately manage the risk at this time. The need for additional risk minimisation activities will be re-evaluated should a safety signal be detected for febrile seizure following D-QIV administration</p>
Bell's Palsy	<p>Close monitoring of all reports of Bell's palsy.</p> <p>Targeted follow-up questionnaire for all reports of Bell's palsy.</p> <p>Reports of Bell's Palsy will be discussed in the PSUR</p>	<p>No specific risk minimisation is needed at this time. The pharmacovigilance activities described in this RMP/PVP appropriately manage the risk at this time. The need for additional risk minimisation activities will be reevaluated should a safety signal be detected for Bell's Palsy following D-QIV administration.</p>
Guillain-Barré syndrome	<p>Close monitoring of all reports of GBS.</p> <p>Targeted follow-up questionnaire for all reports of GBS.</p> <p>Reports of GBS will be discussed in the PSUR.</p>	<p>No specific risk minimisation is needed at this time. The pharmacovigilance activities described in this RMP/PVP appropriately manage the risk at this time. The need for additional risk minimisation activities will be re-evaluated should a safety signal be detected for GBS following D-QIV administration.</p>
<i>Missing information</i>		
Use during pregnancy	<p>Monitoring of all reports involving pregnant females using routine pharmacovigilance.</p> <p>Reports involving pregnant females will be discussed in the PSUR.</p>	<p>A 5 year pregnancy registry will be established after a marketing approval is obtained, with annual report coinciding with the PSUR and final report 18 month after the submission of the final annual report. Information on use of D-QIV during pregnancy is included in proposed product labels. The prescribers are advised that D-QIV should be used during pregnancy only when clearly needed and the possible benefits outweigh the potential risks for the fetus.</p>

Table 10. Summary of Risk management Plan for Fluarix Tetra. continued

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimization activities
<i>Missing information continued</i>		
Use during lactation	Monitoring of all reports involving lactating females using routine pharmacovigilance. Reports involving lactating females will be discussed in the PSUR.	Information on use of D-QIV during lactation is included in proposed product labels. The prescribers are advised that D-QIV should be used during lactation only when clearly needed and the possible benefits outweigh the potential risks.

Pharmacovigilance plan

Routine pharmacovigilance activities were proposed by the sponsor to monitor the Ongoing Safety Concerns associated with Fluarix Tetra (see Table 10 for details). The specified pharmacovigilance plan does not include any clinical study to further evaluate any of the potential risks.

All targeted follow up questionnaires referred to in the European Union (EU) RMP will be implemented in Australia. Following receipt of a completed targeted follow up questionnaire, the sponsor will add any additional information to the case in the global database. This would then be reported to the TGA in the form of a follow-up PSUR.

OPR reviewer's comments

No specific pharmacovigilance activities are planned for Australia.

The evaluator had no objection to the specified pharmacovigilance plan.

Risk minimisation activities

The sponsor proposed routine (product information and labelling) and additional risk minimization activities (5 year pregnancy registry) to mitigate the risks associated with Fluarix Tetra (see Table 10). This was considered acceptable.

The need for additional risk minimisation activities will be re-evaluated should a safety signal be detected from any of the activities described in the RMP/PVP.

The sponsor states in the Australian specific annex:

All of the concerns identified in the EU RMP are relevant for patients in Australia. The risk minimisation activities proposed in the EU RMP will be implemented in Australia. As a routine risk minimisation activity for each of the safety concerns, appropriate wording has been proposed for inclusion in the Australian PI and CMI which is aligned with that described in the EU RMP and included in the proposed SmPC.

It was recommended to the Delegate that additional precautions be added to relevant parts of the proposed Australian PI to further inform prescribers and healthcare professional of the risks for persons with latex sensitivity and lower mean antibody titres in geriatric patients.

The following table summarises the OPR's evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

Table 11. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	<u>OPR evaluator's comment</u>
1. An update on the progress/Sresults/analysis of the registry, as outlined in the RMP, will be expected in future PSURs.	The sponsor confirmed the intention to provide updated information as outlined in the RMP in future PSUR/PBRERs.	This response was acceptable.
2. The sponsor should indicate the location of the proposed 5 year pregnancy registry and whether it will include Australian patients.	GSK has a postmarketing commitment to the US FDA from the approval of the D-QIV (Fluarix Quadrivalent) sBLA to establish a pregnancy registry to prospectively collect data on spontaneously-reported exposures to Fluarix® Quadrivalent during pregnancy. A protocol for this pregnancy registry will be submitted CBER by April 30, 2013. The pregnancy registry will be established in the US by August 3 2013 and annual reports from the registry will be submitted with the periodic safety update reports (PSURs) for Fluarix® Quadrivalent. When the registry has collected data on the outcomes specified in the protocol for five years, GSK will submit a full five year pregnancy registry report, 18 months after the submission of the fifth annual PSUR. After submission of the full five year registry report, GSK will continue enrolling in the registry pending CBER review of the report and determination if the registry can be discontinued. The registry will be established in the US and will not include Australian patients.	This response was acceptable; it was recommended to the sponsor that registry updates are provided annually in the PSUR.
3. An update of the PI to reflect latex sensitivity and lower mean antibody titres in geriatric patients similar to that provided in the FDA prescribing information.	The PI has been updated to reflect latex sensitivity and lower mean antibody titres in geriatric patients, as requested. The description of latex sensitivity has been amended so that it is specific to the presentation planned for supply in Australia, that is, fixed needle presentation containing a protective needle sheath	This response was acceptable.

The OPR evaluator considered that the sponsor's response to the OPR's request for information has adequately addressed all of the issues identified in the First Round RMP evaluation report.

Outstanding issues

Issues in relation to the RMP

There are no outstanding issues in relation to the RMP for this submission.

There is potential for impact of Fluarix Tetra on serology requested for diagnostic purposes for certain infections. The RMP noted the false positive results for enzyme-linked

immunosorbent assay (ELISA) testing for Human immunodeficiency virus 1 (HIV-1), Hepatitis C and human T-cell leukemia virus-1 (HTLV-1). This has the potential to cause unwarranted distress for individuals undergoing immunisation and screening tests. Could the sponsor provide more detailed information on the nature of specific tests that are likely to be affected and what specific activities have been implemented to mitigate and communicate this risk.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

1. Can the committee provide advice on whether the planned routine and additional pharmacovigilance activities and risk minimization activities are adequate to monitor and further inform the identified potential risks, particularly the risk of febrile seizures. If not, could the committee provide advice on alternative mechanisms to strengthen the planned surveillance program?

The committee noted that as most febrile seizures occur between the ages of 6 and 26 months, with the peak at 18 months, the risk had been largely mitigated by the indication being limited to use in children aged over 3 years. In addition, the incidence of fever, the trigger for febrile seizures was similar following Fluarix Tetra compared with the control vaccines and was of the magnitude seen with currently registered vaccines in the vaccine target population. Therefore, ACSOM advised that overall the planned routine and additional pharmacovigilance and risk minimisation activities are adequate to monitor and further inform the identified potential risk of febrile seizures. Furthermore, the risk of off-label use in children under the age of 3 years can be mitigated by appropriate risk communication activities.

The committee expressed concern regarding the proposed monitoring of the potential risk of Bell's Palsy. The committee noted that Bell's Palsy is not a notifiable disease and it is most commonly managed by General Practitioners. In light of this, ACSOM advised that Bell's Palsy may not be detected and reported through the proposed pharmacovigilance activities and it was suggested that sponsor be urged to give more consideration to this in the RMP.

The committee advised that analysis using the self controlled case series (SCCS) method could be undertaken to monitor the potential risks of febrile seizures, Bell's Palsy and Guillain-Barre Syndrome (GBS). However the committee noted such a study may not be feasible given the practicalities with the data capture systems in Australia. In a large exposed patient population a SCCS would need one year to accumulate enough cases of Bell's Palsy and seven years to accumulate enough cases of GBS. A SCCS would also require access to data sources with large enough numbers of exposed subjects to identify rare outcomes, data linkages between the event and the immunisation registry and a way in which to validate events identified in the source data (for example using hospital codes).

The committee also expressed their concerns regarding the potential for impact of Fluarix Tetra on serology requested for diagnostic purposes for certain infections. They noted that this has led to false positive results for ELISA testing for HIV-1, Hepatitis C and HTLV-1 and the implications this may have for individuals undergoing immunisation and screening tests (for example, healthcare workers) in terms of causing unwarranted distress and concerns. ACSOM advised that the TGA should request more detailed information from the sponsor regarding the nature of specific tests that are likely to be affected and that specific activities be implemented to mitigate and communicate this risk.

Suggested wording for conditions of registration

RMP

Implement RMP (EU RMP Version 1, date: 2 February 2012, data lock point: 9 September 2011) +/- Australian-Specific Annex and any future updates as a condition of registration.

PSUR

An obligatory component of Risk Management Plans is Routine Pharmacovigilance. Routine Pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs). Reports are to be provided annually until the period covered by such reports is not less than three years from the date of this approval letter. No fewer than three annual reports are required. The reports are to at least meet the requirements for Periodic Safety Update Reports (PSURs) as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-Periodic Safety Update Report, Part VII.B. "Structures and processes". Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

The annual submission may be made up of two Periodic Safety Update Reports each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The administrative, product usage, chemical, pharmaceutical, microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA. No outstanding quality issues remain. Consistency of production has been demonstrated over two manufacturing buildings.

This is the first quadravalent Influenza vaccine to be registered in Australia. The vaccine contains approximately 30% more detergent than the TIV, 15 µg more HA antigen and an increase in NA antigen. Residual amounts of formaldehyde and ovalbumin remain the same as the TIV. At the upper level of specifications for detergent concentration the SRD potency assay was found not to conform. The sponsor plans to either revalidated the assay or tighten detergent specifications prior to commencement of commercial production. The quality evaluator(s) recommend that for Fluarix tetra 1 x, 10x 15 µg/dose/strain HA 25 G 5/8 needle attached and PRTC syringe, a shelf life of 9 months and 12 months respectively should be approved.

The evaluator stated that it is a condition of registration that all independent batches of Fluarix tetra 1x, 10x15 µg/dose/strain HA 25G needle attached and PRTC syringe imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services. An electronic draft of the Certified Product Details (CPD), as described in Appendix 7 of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM)²², should be provided upon registration of these therapeutic goods. In

²² Guidance 7: Certified product details <<http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm>>

addition, an updated CPD should be provided when any changes to finished product specifications and test methods are approved.

Nonclinical

No nonclinical protective efficacy studies were submitted, and immunogenicity data in mice and ferrets were inconclusive. The nonclinical evaluator commented that the demonstration of vaccine efficacy and immunogenicity will depend on clinical data. Acute and repeat dose toxicity studies in rabbits with the QIV and related trivalent influenza vaccine (TIV) did not reveal any vaccine-related toxicity and local inflammation at injection sites was minor and transient. Reproductive and developmental toxicity studies in rats with the QIV and related TIVs revealed no vaccine related toxicity. An Australian Pregnancy Category of B1 was recommended. Adequate multiples of the human dose, on a mg/kg basis for both adults and children, were administered in all toxicity studies. There were no nonclinical objections to registration, provided that the clinical data demonstrate satisfactory vaccine efficacy/immunogenicity. The evaluator recommended a number of amendments to the Product Information.

Clinical

Pivotal Study FLU-D-QIV-008 (in adults)

This was a Phase III, partially-blind, controlled, parallel group study. The study evaluated the safety and immunogenicity of D-QIV vaccine in adults 18 years of age and over, who were either healthy or had chronic well-controlled disease. The primary objectives of the study were to assess:

1. Lot-to lot consistency of HI antibody GMTs of three lots of the quadrivalent influenza vaccine D-QIV.
2. Non-inferiority in terms of HI antibody GMTs and seroconversion rates of D-QIV compared to trivalent influenza vaccine TIV-1 (Brisbane) and TIV-2 (Yamagata) vaccine for the three strains that were included in each of the two trivalent vaccines.
3. Superiority in terms of GMTs and SCRs of the D-QIV vaccine compared to the two trivalent vaccines for the B strain that was not included in each vaccine.

A total of 4656 individuals were vaccinated in this study and participants were randomised into 5 groups (5:5:5:5:3). From the 3036 individuals vaccinated with three different lots of the candidate D-QIV vaccine, 1012 were vaccinated in the D-QIV-1 group, 1013 in the D-QIV-2 group and 1011 in the D-QIV-3 group; 1010 participants were vaccinated with Fluarix including the B/Victoria, and 610 with TIV-2 vaccine which was identical to Fluarix except for inclusion of the B/Yamagata. Demographics were evenly spread in these groups. The age range was from 18 to 92 years. Over two thirds were White Caucasian and approximately a quarter was East Asian. Withdrawal rate was less than 2%. Lot-to-lot constancy was shown for all three lots. Non-inferiority criteria for HI antibody GMTs and seroconversion rates were met for all vaccine strains shared with the trivalent vaccines. Criteria for superiority of D-QIV to TIVs for the B-strains not included in the trivalent vaccines were also met.

Secondary objectives were to describe the immunogenicity in terms of GMTs and seroprotection rate (SPR) at Days 0 and 21 and seroconversion rate (SCR) and mean geometric increase at Day 21 and to assess reactogenicity and safety. Baseline seropositivity rates were similar across vaccination groups. The lowest seropositivity rate was for the H1N1 component of the vaccine (53.7% to 58.2%). For H3N2, the rates were approximately 80%, for B virus Victoria lineage rates were approximately 85% and for the

Yamagata lineage approximately 86%. For each strain and each vaccine, SCR, SPR and mean geometric fold increases met the criteria for adults 18 to 60 years of age as defined in CPMP/BWP/214/96 *Harmonisation of Requirements for Influenza Vaccines guidelines*.²⁰

The clinical evaluator considered that this study was well designed and the results support that the quadrivalent vaccine is sufficiently immunogenic to recommend registration for use in adults from 18 years of age.

Supportive Study FLU-D-QIV-001 (in adults)

This was a Phase I/II dose finding, single blind, controlled study conducted in adults to assess the immunogenicity, safety and reactogenicity of the quadrivalent influenza candidate vaccine.

The co-primary objectives relevant to the appraisal of D-QIV were assessment of non-inferiority of HI GMTs of D-QIV versus Fluarix for the three seasonal strains and superiority of HI GMT of D-QIV versus Fluarix for the B/Jiangsu/10/2003 strain not included in Fluarix. Criteria for non-inferiority were met for the three strains included in the seasonal trivalent vaccine. Superiority in protocol defined terms was demonstrated for the strain not included in Fluarix.

Participants aged 19 to 59 years were randomised 1:1:1:1 to four groups of 105 participants. The groups were vaccinated with D-QIV or Fluarix or with a low dose adjuvanted quadrivalent or trivalent vaccine. The quadrivalent vaccine included B/Malaysia/2506/2004 and B/Jiangsu/10/2003. The seasonal vaccine included the B/Malaysia strain. Only one participant withdrew from the study and two were excluded from the ATP analyses.

Secondary objectives included assessment of humeral immune responses. Baseline seropositivity rates were similar for all vaccine groups and were relatively high: approximately 60% for A/Solomon/H1N1, approximately 80% for A/Wisconsin/H3N2, between 75% 82% for D-QIV and TIV respectively for B/Malaysia and approximately 70% for B/Jiangsu. For D-QIV, SCR, SPR and mean geometric fold increases met the CPMP criteria for adults 18 to 60 years.

This study was considered to have been well conducted and reported. The results support that this vaccine is sufficiently immunogenic to recommend registration for the age group included in the study. The GMT results did not suggest interference.

Supportive Study Fluarix-US-006 (vaccine efficacy in adults)

Fluarix -US-006 was a Phase IV, randomized, double-blind, placebo-controlled, multi-country and multi-center study. The study assessed the efficacy of Fluarix 0.5 mL administered IM (intramuscularly) in adults aged 18-64 years old. The study was conducted during the Northern Hemisphere season 2006/2007. A total of 7652 participants were randomised 1:1:1 to receive Fluarix lot 1, Fluarix lot 2 or placebo (normal saline). The mean ages for the two groups were 40.0 and 39.7 years, the majority of subjects (60%) in each group were female and the population was predominantly White Caucasian (99.9%). The withdrawal rate was less than 3%.

The primary objective was to demonstrate the efficacy of Fluarix in the prevention of culture confirmed influenza A and/or B cases for vaccine antigenically matched strains compared to the placebo group. The primary objective was met if the lower limit of the 95% confidence interval (CI) for the vaccine efficacy against culture-confirmed influenza A and/or B, for vaccine antigenically matched strains, was above 35%. Active surveillance for influenza like illness was conducted by the investigator approximately bi-weekly during the study period starting from 2 weeks after vaccination until the end of the influenza season. There was a 14 day follow-up period for each ILI episode. Influenza like

illness was defined as at least one systemic symptom, fever (oral temp $\geq 37.8^{\circ}\text{C}$) and/or myalgia and at least one respiratory symptom. The first day of an ILI episode was defined as the first day with one systemic symptom and one respiratory symptom. The last day of an ILI episode was defined as the last day either with fever, myalgia, cough or sore throat. A new ILI episode was only to be taken into account after the complete resolution of the previous one. Between two ILI episodes, there had to be at least 7 days free of any symptoms. A swab of both nares and a throat swab were collected at the onset of the ILI for influenza virus culture and identification, classification of influenza A and/or B virus isolates as “vaccine matching” or not, by serological typing and testing for influenza A and/or B by RT-PCR. A diagnosis of pneumonia was confirmed by chest X-ray.

Efficacy analysis was performed on the Total Vaccinated Cohort (TVC, the primary analysis), According to Protocol (ATP) cohort – from 2 weeks post vaccination (used for all endpoints except ILI), and the ATP cohort for analysis of efficacy – influenza season (used for the ILI endpoint only). There were 145 subjects with ILI who had culture-confirmed influenza A and/or B [63 Fluarix subjects (1.2%) and 82 placebo subjects (3.2%)]. Characterisation of virus isolates from the culture confirmed ILI cases indicated that the majority were influenza A H3N2 with most typed as matching the vaccine strain. The attack rate of 2.9% in the placebo group was in line with the assumed attack rate of 2% on which the sample size estimation was based. The lower attack rate in the Fluarix group resulted in a statistically significant vaccine efficacy (VE) estimate of 66.9% ($p < 0.001$). As the lower limit of the CI for the vaccine efficacy (VE = 51.9%) was above 35%, the primary objective of the study was met.

The clinical evaluator was of the view that the result of this study supports the efficacy of Fluarix in adults.

Pivotal Study FLU-D-QIV-003(in paediatrics)

This was a Phase III, randomised, controlled, multi-country, multi-centre study conducted in children 3 to 17 years. The primary objective of the study was to demonstrate immunological non-inferiority of D-QIV versus TIV-1 containing B/Victoria lineage and TIV-2 containing B/Yamagata lineage, in terms of GMT and SCR 28 days after completion of the vaccination series (Day 28 for primed individuals, Day 56 for unprimed participants). Evaluation of immunological superiority in terms of GMTs and SCR, of D-QIV versus TIV-1 and TIV-2 for the B strain not contained in each TIV formulation was a secondary objective. Other secondary objectives were to describe the immunogenicity in terms of GMTs, SPR, SCR and mean geometric increase and to assess reactogenicity and safety.

A total of 2741 participants aged 3 to 17 years were randomised 1:1:1 to receive D-QIV, TIV-1 (Fluarix with B/Victoria) or TIV-2 (with B/Yamagata). Primed participants were vaccinated with one intramuscular injection on Day 0. By protocol definition, primed participants had received at least one dose of an influenza A (H1N1) 2009 monovalent vaccine in the previous season or had laboratory confirmed H1N1 infection *and* had received two doses of seasonal influenza immunization separated by at least one month during last season or had received at least one dose prior to last season.

Two injections at Day 0 and Day 28 were given to unprimed participants. By protocol definition, these children had not received any influenza A (H1N1) 2009 monovalent vaccine in the last season or did not have laboratory confirmed H1N1 infection *or* had not previously received any seasonal influenza immunization in the past or received only one dose of influenza vaccine for the first time in the last influenza season.

Demographics were similar across the 3 groups. The population included approximately 56% White Caucasians, approximately 26% South East Asians and approximately 13% African Americans. Over 5% were eliminated from the ATP immunogenicity population;

therefore, analyses were conducted on the ATP and the TVC populations. A fourth group, D-QIV-Y, aged 6 to 35 months was also included in the study. Immunogenicity results for this group were not evaluated in this report; however the group was examined for safety. The study objectives were based on results from participants 3 to 17 years of age.

The primary objectives were met. Non-inferiority of D-QIV versus Fluarix and TIV-2 and D-QIV versus TIV-2 for the common antigens was demonstrated. Superiority of D-QIV versus the two TIV vaccines was demonstrated for the B strain not included in the TIV vaccines.

Baseline seropositivity rates were between 63.5% and 68.9% for A (H1N1), between 76.1% and 79.4% for A (H3N2), approximately 75% for B (Victoria) and 92% for B (Yamagata). GMTs rose postvaccination for all antigens but more so for antigens contained in the vaccines. Seroprotection rates post vaccination were high and met the CPMP criteria for adults 18 to 60 years for all antigens included in the vaccines and for B/Brisbane not contained in the TIV-2 vaccine. Seroprotection rate for the B/Yamagata strain not contained in TIV-2 met the criterion for adults over 60 years of age. Mean fold changes met the CPMP criterion for adults 18 to 60 years for all antigens, irrespective of inclusion in a particular vaccine; however, fold rises were considerably higher for antigens included in the vaccines.

The evaluator considered that this study was well conducted and reported. The results of the study support the opinion that immunogenicity was sufficient to recommend registration.

Supportive Study FLU-D-QIV-002(in paediatric patients)

This was a Phase II, double-blind, multicentre, randomised study evaluating immunogenicity, reactogenicity and safety of D-QIV compared with the Fluarix, in children 18 to 47 months of age. The primary objective of the study was to demonstrate the immunological non-inferiority of D-QIV for the 3 recommended seasonal strains. Assessment of superiority of D-QIV compared to TIV for the B strain not included in the trivalent vaccine was a secondary objective.

A total of 599 children were randomised 1:2:1:2 into four groups with approximately 100 children in each of the D-QIV and TIV primed group and 200 in each of the D-QIV and TIV unprimed groups. By study definition, unprimed children had not been vaccinated with 2 doses of influenza vaccine in the previous season and received two doses of vaccine in the study. Primed children had previously received 2 doses of Fluarix 0.5 mL in the GSK Biologicals' study Fluarix-US-007 the preceding season and were vaccinated with one dose in Study D-QIV-002. The B virus lineage of the priming vaccine could not be determined and thus was inferred from results.

The primary objective was met for the three recommended seasonal strains according to the protocol. Superiority was demonstrated for the B strain not included in the TIV vaccine. Baseline seropositivity results were higher for the primed participants than for the non-primed, even for the B strain not included in the priming vaccine; however, seropositivity result for the B strain not included in the priming vaccine for both primed and unprimed children was considerably lower than for other strains.

Seroconversion rates for A/H1N1 met the CPMP criterion for adults 18 to 60 years except for primed participants in the D-QIV group which met the criterion for adults over 60 years of age. For A/H3N2 and B/Victoria, the criterion was met for all groups. For B/Yamagata, the result was better for D-QIV but still passed the CPMP criterion for participants in the TIV group who were not vaccinated with the B/Yamagata strain. Fold increases met the CPMP criterion for adults 18 to 60 years for all antigens and were higher in the unprimed than the primed participants.

Seroprotection rates for B/Victoria met the CPMP criterion for adults 18 to 60 years for both unprimed groups but both primed groups failed to reach the CPMP criteria for adults 18 to 60 years and the CPMP criteria for elderly (> 60 years). For the B/Yamagata strain, results met the CPMP criterion for adults 18 to 60 years for all but the TIV unprimed group which met the criterion for adults over 60 years.

The clinical evaluator was of the view that although the children in this study were generally younger than those for whom the indication is proposed, there was a proportion between 36 and 47 months of age, relevant to this application. These children were not separately analysed. The overall results suggest that young children previously vaccinated with a trivalent vaccine may benefit from two doses at first vaccination with the quadrivalent vaccine.

Clinical safety evaluation

Safety in adults

A total of 3,036 adults were exposed to at least one dose of D-QIV vaccine in Study D-QIV-008 and 105 adults in Study D-QIV-001. No new or unexpected safety signal was detected. In the pivotal study, the safety profile in the D-QIV vaccinated groups is similar to that in the TIV vaccinated groups. The incidences of solicited AEs were generally similar following D-QIV and Fluarix except for injection site pain in supportive Study D-QIV-001, where pain was more common in the D-QIV group (72.4%) than in the Fluarix TIV group (49.5%). In Study D-QIV-008, pain at the injection site was reported by a similar percentage of individuals in the D-QIV group (36.4%) and the TIV-1 and TIV-2 groups (36.8% and 31.3% respectively). In Study D-QIV-008, grade 3 pain was reported in 0.5%-1.2% of individuals across the 3 vaccine groups. Redness and swelling were reported by 1.3% to 2.1% of individuals. The sponsor considered that the smaller number of participants in D-QIV-001 may have biased the results for pain. The evaluator noted that Study D-QIV-001 was not double blind.

In both adult studies, fatigue, myalgia and headache were the most common solicited general symptoms. Incidences of fatigue and headache were higher in supportive Study D-QIV-001 than in the large pivotal Study D-QIV-008, particularly so for fatigue. Examining each study separately, the incidences of events were similar for included vaccine groups. For D-QIV-008 results were; myalgia: D QIV 16.4%, TIV-1 19.4% and TIV-2 16.1%; fatigue: D-QIV 15.8%, TIV-1 18.4% and TIV-2 14.8% and headache: D-QIV 15.9%, TIV-1 16.4% and TIV-2 13.2%. For D-QIV-001 results were: myalgia: D-QIV 16.2% TIV 14.3%, fatigue: D-QIV 31.4%, TIV 32.4% and headache: 23.8%, TIV 24.8%. Grade 3 solicited general events were reported by a maximum of 2.9% of participants, the maximum being for headache in the D-QIV group in supportive Study D-QIV-001. Lower reactogenicity was seen in participants aged ≥ 65 years in Study D-QIV-008 compared with those aged 18 to 64 years.

The most frequently reported unsolicited AEs were nasopharyngitis, cough and oropharyngeal pain in Study D-QIV-008 and pharyngitis and headache in Study D-QIV-001; all reported at incidences lower than 2.0% in each vaccine group. Few unsolicited AEs were considered vaccine-related, the most common being injection site haematoma and oropharyngeal pain in Study D-QIV-008, reported in 0.2-0.5% of individuals. Severe (Grade 3) AEs after D-QIV vaccination were reported by 1.3% of individuals in Study D-QIV-008 and none in D-QIV-001.

There were no deaths, serious adverse events discontinuations or potential immune mediated diseases considered related to study vaccine.

The clinical evaluator was of the view that in adults, the safety and reactogenicity of D-QIV was similar to that of Fluarix.

Safety in paediatrics

A total of 1192 children from 6 months to 17 years of age were exposed to at least one dose of D-QIV vaccine in the Phase III D-QIV-003 study; 915 of whom were in the 3 to 17 years age group. Safety data were available for 534 children who received one dose and 956 children who received two doses of the D-QIV vaccine. An additional 298 children from the supportive study D-QIV-002 contributed safety information.

The most common solicited local AE was injection site pain reported by approximately 40%-50% of participants across all studies groups. Grade 3 pain was reported by 0.2% to 2.3%. Redness and swelling were less common and were reported at similar rates across the vaccine groups in both studies. Pain tended to be reported by fewer participants aged 6 to 35 months (30.5%) than in children aged 3 to 17 years, possibly related to developmental language ability, while a trend to more reports of redness (28.4%) was observed in the youngest group.

In children aged 6 to 17 years (Study D-QIV-003), the most frequently reported solicited general symptoms were fatigue, muscle aches and headache, all reported with frequencies ranging from 16.9% to 21.2% across the different groups.

The incidences of solicited general AEs were similar across all study groups in Study D-QIV-003, regardless of severity and causal relationship. For children < 6 years (3 to 5 years in D-QIV-003, 18 to 47 months in D-QIV-002), loss of appetite, irritability and drowsiness were reported for 20.3% to 30.7% of the D-QIV vaccinated children in both studies. Fever was recorded for 17.2% and 25.3% of D-QIV participants in Studies D-QIV-003 and D-QIV-002, respectively. Overall, the incidences of all local and general solicited symptoms were similar following vaccination with D-QIV and the trivalent comparators. The incidences of solicited general AEs, including fever, in children aged 6 to 35 months who received D-QIV vaccine in Study D-QIV-003, were within the same range as in children aged 18 to 47 months in Study D-QIV-002, but were generally higher than in children aged 3 to 17 years in D-QIV-003. Grade 3 fever reports followed 3.9% of doses in 6.5% of individuals in the youngest age ranges.

In Study D-QIV-003 for children aged 3-17 years, fever (defined as rectal temperature $\geq 38^{\circ}\text{C}$, oral or axillary temperature $\geq 37.5^{\circ}\text{C}$) was reported for 10.8% of individuals in the D-QIV group, compared to 12.3% in the Fluarix group and 9.4% in the TIV-2 group. The incidence of fever $>38^{\circ}\text{C}$ was 4.6% in the D-QIV group, 4.9% in the Fluarix group and 3.5% in the TIV-2 group. Grade 3 fever defined as $> 39^{\circ}\text{C}$ was reported in 1.8% of individuals in the D-QIV group, 1.1% in the Fluarix group and 0.8% in the TIV-2 group.

Febrile convulsions were considered events of specific interest in Study D-QIV-003. Two cases of febrile convulsion were reported, both from the D-QIV-Y group. Both cases were reported as SAEs, neither was reported within 2 days postvaccination enhanced surveillance period and neither was considered related to vaccination. In Study D-QIV-002, one case of febrile convulsion was reported in the D-QIV group and was not considered related to vaccination.

In those participants who received two doses, there was no evidence of an increased incidence of solicited AEs following the second dose compared to the first dose. Grade 3 solicited events were reported following $\leq 1.6\%$ of doses across vaccine groups from both studies.

Few unsolicited AEs were considered vaccine related ($\leq 2.3\%$ after D-QIV vaccination). Severe (Grade 3) unsolicited AEs were reported for D-QIV: in 2.2% (3 to 17 years), 3.4% (18 to 47 months) and 7.2% (6 to 35 months). In both paediatric studies, no differences between D-QIV and comparators were observed.

There was no serious adverse event (SAE) which was considered vaccine related. In Study D-QIV-003, 3 individuals discontinued the study because of an unrelated SAE or AE. One

individual in the Fluarix group died due to a road traffic accident; one in the D-QIV group was withdrawn due to non-fatal bacterial gastroenteritis; one in the Fluarix group was withdrawn due to non-serious viral pneumonia. Two potential immune mediated diseases were reported in study D-QIV-003, one case of non-serious Bell's palsy and one serious case of type 1 diabetes mellitus were reported. Neither was considered vaccine related.

The clinical evaluator was of the view that the safety and reactogenicity of D-QIV was found to be similar to that of Fluarix in the paediatric subjects from 3 years of age.

Clinical evaluator's conclusion

The immunogenicity of Fluarix Tetra has been demonstrated in adults and children from 3 years of age. The safety of Fluarix Tetra studied in the age groups proposed for registration appears to be similar to that of the registered trivalent vaccines. Clinical efficacy of Fluarix Tetra has not been determined. The risk benefit balance was considered to be on the side of benefit. Registration of Fluarix Tetra was recommended.

Risk management plan

The submitted RMP was evaluated by an OPR evaluator. The evaluator states that there are no outstanding issues in relation to the RMP for this submission.

ACSOM advice

ACSOM advice was sought for this application. The committee noted that as most febrile seizures occur between the ages of 6 and 26 months with the peak at 18 months, the risk had been largely mitigated by the indication being limited to use in children aged over 3 years. In addition, the incidence of fever, the trigger for febrile seizures, was similar following Fluarix Tetra compared with the control vaccines and was of the magnitude seen with currently registered vaccines in the target population. Therefore, ACSOM advised that the planned routine and additional pharmacovigilance and risk minimisation activities are adequate to monitor and further inform the identified potential risk of febrile seizures. Furthermore, the risk of off-label use in children under the age of 3 years can be mitigated by proper risk communication activities. The committee expressed concern regarding the proposed monitoring of the potential risk of Bell's Palsy. The committee noted that Bell's Palsy is not a notifiable disease and it is most commonly managed by General Practitioners. In light of this, ACSOM advised that Bell's Palsy may not be detected and reported through the proposed pharmacovigilance activities and it was suggested that sponsor be urged to give more consideration to this in the RMP. The committee also expressed their concerns regarding the potential for impact of Fluarix Tetra on serology requested for diagnostic purposes for certain infections, as the use of Fluarix Tetra has lead to false positive results for ELISA testing for HIV-1, Hepatitis C and HTLV-1 and the implications this may have for individuals undergoing immunisation and screening tests (such as healthcare workers) in terms of causing unwarranted distress and concerns. ACSOM advised that the TGA should request more detailed information from the sponsor regarding the nature of specific tests that are likely to be affected and that specific activities be implemented to mitigate and communicate this risk.

Risk-benefit analysis

Delegate considerations

The Delegate agreed that the submitted data support the acceptable immunogenicity and safety of Fluarix Tetra in persons 3 years and older. It is noted that no clinical efficacy

studies were conducted with Fluarix Tetra. The clinical efficacy demonstrated for Fluarix (see Fluarix-US-006) provides some support for the likely clinical efficacy of Fluarix Tetra. If approved, Fluarix tetra will be the first quadrivalent influenza vaccine registered in Australia.

It is expected that the adding an additional B antigen will likely increase the cost of the vaccine and the time required for vaccine production. It is not known whether these additional efforts will bring additional clinical benefit.

The changes to the initially proposed PI have been recommended from various evaluation areas of the TGA. The sponsor should include a revised version of the PI with the Pre-Advisory Committee on Prescription Medicines (ACPM) response. Further changes to the PI may be required prior to the finalisation of this application, taking into account the discussion and the advice from the ACPM meeting as well as relevant Prescribing Information approved by overseas regulatory agencies.

Delegate's Pre ACPM proposal

The Delegate had no reason to say, at this stage, that the application for Fluarix Tetra should not be approved for registration for the indication proposed below:

Fluarix Tetra is a quadrivalent vaccine indicated for active immunisation of adults and children from 3 years of age for the prevention of influenza disease caused by the influenza virus types A and B contained in the vaccine.

The use of Fluarix Tetra should be based on official recommendations.

If approved, the implement RMP (EU RMP Version 1, date: 2 February 2012, data lock point: 9 September 2011) +/- Australian-Specific Annex and any future updates will be imposed as a condition of registration. The conditions of registration also include the requirements listed by the quality evaluator.

Issues requesting ACPM advice

The Committee was requested to comment

- on whether Fluarix Tetra is likely to have additional clinical benefit over Fluarix, the registered trivalent influenza vaccine.
- and give advice on any issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Delegates questions:

1. Comment on whether Fluarix Tetra is likely to have additional clinical benefit over Fluarix, the registered trivalent influenza vaccine.

The Fluarix Tetra influenza vaccine includes two influenza A subtype viruses (H1N1 and H3N2) and two type B viruses (one from the Yamagata lineage and one from the Victoria lineage). The two influenza A viruses and one of the influenza B viruses are identical to those contained in Fluarix (the TGA registered trivalent influenza vaccine). All strains in Fluarix Tetra are produced according to the same manufacturing process as the current-approved Fluarix.

As concluded by the TGA Delegate and TGA clinical evaluator, the clinical data package submitted in support of registration of Fluarix Tetra demonstrates the following in subjects aged 3 years and above:

- non-inferiority of the haemagglutination-inhibition (HI) immune response elicited by Fluarix Tetra to that induced by Fluarix (and an alternate trivalent formulation) for the three strains common to both vaccines;
- superiority of the HI immune response of Fluarix Tetra recipients to that displayed by trivalent vaccinees, against the additional B strain included in Fluarix Tetra.

The clinical data package includes a safety database of more than 3,000 adults and more than 1,200 children. As concluded by the TGA Delegate and TGA Clinical Evaluator, the safety results demonstrate that the reactogenicity and safety profile of the quadrivalent Fluarix Tetra is similar to that of the trivalent Fluarix.

For these reasons the TGA Delegate and TGA clinical evaluator recommended approval of Fluarix Tetra for the requested Indication.

2. The Delegate requested ACPM's advice on whether Fluarix Tetra is likely to have additional clinical benefit over Fluarix.

GSK provides the following comments in response to this.

Globally, the evidence of influenza B disease burden is growing. Whilst the sponsor acknowledged that there are gaps in the understanding of the scale of the burden of influenza B disease worldwide, there is ample evidence that demonstrates influenza B can pose a significant burden to the global population.²³ For example, 16% of the influenza associated deaths in the overall population in the US from 1990 to 1999 (8,349) were due to influenza B.²⁴ Eighty-six percent of these influenza B deaths occurred in the elderly (≥ 65 years of age), where they represent 16% of all influenza-related deaths. Although influenza B mortality is prominent in the elderly, paediatric deaths due to influenza B also occur and represented 46% of all influenza related deaths in children below the age of 5 years during this same period.²⁴

In Australia, over the past decade to 2011, the proportion of all influenza cases caused by influenza B has varied widely from year to year. The table below shows that between 2000 and 2011, influenza B viruses made up 22.2% of all influenza on average, with a range from 0.8% in 2003 to 63.3% in 2008.³ In 2012, 9,096 (22.0%) of reported influenza cases were influenza B.²⁵

²³ Paul Glezen W, Schmier JK, Kuehn CM, Ryan KJ, Oxford J. The burden of influenza B: a structured literature review. *Am J Public Health*. 2013 Mar;103(3):e43-51.

²⁴ Thompson WW, Shay DK, Weintraub E et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA* 2003;289:179-186.

²⁵ Australian Department of Health and Ageing. Australian Influenza Surveillance Report 2012;10. Available at <[http://www.health.gov.au/internet/main/publishing.nsf/Content/B2480F91BA77471FCA257AA2001DFF5B/\\$File/ozflu-no10-2012.pdf](http://www.health.gov.au/internet/main/publishing.nsf/Content/B2480F91BA77471FCA257AA2001DFF5B/$File/ozflu-no10-2012.pdf)>

Table 12. Circulation of influenza B virus lineages in Australia 2001-2011.

Year	Influenza B as proportion of all influenza	B/Yamagata lineage as proportion of influenza B	B/Victoria lineage as proportion of influenza B	B lineage in Trivalent vaccine	Vaccine match to circulating B viruses
2000 ⁵	33.1%	100%	0	Yamagata	Complete
2001 ⁶	14.5%	100%	0	Yamagata	Complete
2002 ⁷	22.8%	4.0%	96.0%	Yamagata	Low
2003 ⁸	0.8%	80.0%	20.0%	Victoria	Low
2004 ⁹	25.0%	83.3%	16.7%	Victoria	Low
2005 ^{10,11}	21.5%	51.7%	48.3%	Yamagata	Partial
2006 ¹²	34.4%	4.5%	95.5%	Victoria	High
2007 ¹³	5.3%	78.0%	22.0%	Victoria	Low
2008 ^{14,15}	63.3%	48.8%	51.2%	Yamagata	Partial
2009 ¹⁶	1.2%	38.5%	61.5%	Yamagata	Partial
2010 ^{17,18}	12.7%	9.2%	90.8%	Victoria	High
2011 ^{19,20}	31.2%	1.8%	98.2%	Victoria	High

[Note: because laboratory-confirmed influenza cases represent a small proportion of the total, estimates for each year are based on small samples.]

The relative proportions of the two antigenically distinct B lineages (B/Yamagata and B/Victoria) have also fluctuated unpredictably in Australia during this period.²⁶ Importantly, in 2008, when influenza B was the dominant circulating influenza strain, both B lineages co-circulated in almost equal proportions, meaning that the trivalent influenza vaccine for that year provided coverage for less than half of the circulating B viruses.^{25, 26} Between 2000 and 2011, there was a major mismatch between the recommended vaccine virus and the circulating B-lineage virus in 4 of the 12 years analysed, with a partial match in 3 years, and a good match in only 5 of the 12 years.²⁶

These data clearly indicate that influenza B represents a significant proportion of the overall burden of influenza in Australia, and that the B strain selected each season for the trivalent vaccine has often not matched the circulating strains causing disease in the community.

In the clinical studies included in the submission, Fluarix induced a degree of cross reactive immune response to the B strain not contained in the TIV, however Fluarix Tetra was shown to induce superior immune responses against the additional B strain without impairing the response to the other three strains contained in the trivalent vaccine. This is affirmed by the TGA Delegate and TGA clinical evaluator in their assessments of the clinical data package. Anti-haemagglutinin (HI) antibodies are widely acknowledged to be a strong predictor of protection²⁷; this is despite the absence of clear correlates of protection against influenza viruses. Therefore, since the quadrivalent vaccine induces broad immunity, measured by high titres of HI antibodies against all four strains in the vaccine, Fluarix Tetra can reasonably be anticipated to offer broader protection than the currently registered trivalent vaccines.

Importantly, this broader protection is offered without compromising the safety of the vaccine, since the safety profile for Fluarix Tetra and Fluarix are very similar.

²⁶ Barr IB, Jelley LL. The coming era of quadrivalent human influenza vaccines: who will benefit? *Curr Op Drugs* 2012; 72 (17): 2177–2185.

²⁷ Ohmit SE et al. Influenza hemagglutination-inhibition antibody titer as a correlate of vaccine-induced protection. *J Infect Dis*. 2011;204:1879—85.

The additional clinical benefit of the second B strain in the quadrivalent influenza vaccine is difficult to demonstrate conclusively in a clinical trial. Ideally, a very large comparative efficacy trial with both quadrivalent and trivalent would be conducted over several seasons, to include those seasons with a high prevalence of influenza B, mismatched to trivalent. Together with an analysis of factors such as vaccination history of subjects, this strategy could help to assess the extent to which the limited immune cross-reactivity observed against the B strain not contained in Fluarix translates to cross-protection in the real world.

However, since an extremely large trial of this nature would be difficult to successfully conduct, partly due to the unpredictable fluctuation of seasonal strains, GSK has conducted a systematic review of 34 randomised clinical trials of trivalent influenza vaccines, including more than 94,000 adults.²⁸ The calculated vaccine efficacy (VE) against matched influenza B strains was 77% (95% CI 18-94), whereas VE against mismatched influenza B strains was 52% (95% CI 19-72).²³ Another recent systematic review and meta-analysis included 30 controlled efficacy trials and more than 88,000 participants.²⁹ The estimate for VE against matched B strains was 71%, whereas the VE estimate against non-matched strains was 49%.²⁹ In summary, these analyses show that trivalent vaccines are less effective when they are not matched to circulating strains, and therefore that the observed immune cross-reactivity against the B strain not included does not provide optimum clinical protection. Cross-reactivity can also be expected to reduce further over time as the two influenza B lineages continue to diverge under selection pressure.³⁰

Therefore, the inclusion of a second B strain in seasonal vaccines is a way to improve prevention of influenza, by ensuring the B strain match of the vaccine irrespective of the B strain in circulation. Fluarix Tetra therefore offers broader protection than the currently registered trivalent vaccine. Broader immunity measured by HI antibody titres, can reasonably be anticipated to be correlated with a better protection.

In conclusion, the sponsor's position is that the risk-benefit ratio of Fluarix Tetra is positive and that compared with trivalent vaccines, the quadrivalent influenza vaccine offers broader direct protection from constantly changing influenza viruses.

Risk management plan

The Sponsor noted the comments from the OPR relating to the Risk Management Plan regarding the potential for impact of Fluarix Tetra on serology requested for diagnostic purposes for certain infections. Although the RMP noted the false positive results for ELISA testing for HIV-1, Hepatitis C and HTLV-1, the evaluator felt this had the potential to cause unwarranted distress for individuals undergoing immunisation and screening tests. The sponsor was asked to provide more detailed information on the nature of specific tests that are likely to be affected and what specific activities have been implemented to mitigate and communicate this risk.

In response, the sponsor noted that false positive ELISA serological screening tests for HIV-1, Hepatitis C, and HTLV-1 may occur following influenza vaccination. The transient false-positive reactivity for antibodies to HIV, HTLV-I and hepatitis C in association with influenza vaccination was first observed in 1991 and has been attributed to serum immunoglobulin M (IgM) (which is not specific for these viruses) binding to and cross-reacting with test kit components. This issue was largely associated with early generation

²⁸ Tricco AC et al. Comparing influenza vaccine efficacy against mismatched and matched strains: a systematic review and meta-analysis. *BMC Medicine* 2013;11:153 doi:10.1186/1741-7015-11-153

²⁹ DiazGranados CA et al. Seasonal influenza vaccine efficacy and its determinants in children and non-elderly adults: a systematic review with meta-analyses of controlled trials. *Vaccine* 2012;31: 49-57.

³⁰ Xu J et al. Evolutionary history and phylodynamics of Influenza A and B Neuraminidase (NA) genes inferred from large-scale sequence analyses. *PLoS ONE* 2012;7(7): e38665. doi:10.1371/journal.pone.0038665

HIV ELISA test kits, which were highly sensitive but not highly specific for this virus.³¹ Although these kits are no longer marketed globally, one cannot exclude the possibility that these kits are being used in low-resource settings. False positives with screening Hepatitis C and HTLV-1 tests are still possible. The FDA as well as WHO recommend confirmatory testing such as Western blot or polymerase chain reaction (PCR) testing after initial ELISA screening.

Therefore, in regard to the specific activities implemented to mitigate and communicate this risk, GSK has included a statement in the *Precautions* section of the PI, as follows:

False positive ELISA serologic tests for HIV-1, Hepatitis C, and especially HTLV-1 may occur following influenza vaccination. These transient false-positive results may be due to cross-reactive IgM elicited by the vaccine. For this reason, a definitive diagnosis of HIV-1, Hepatitis C, or HTLV-1 infection requires a positive result from a virus-specific confirmatory test (e.g. Western Blot or immunoblot).

Sponsor's conclusion

The company agreed to the Delegates recommendations to implement the RMP (EU RMP Version 1, date: 2 February 2012, data lock point: 9 September 2011) +/- Australian-Specific Annex and any future updates as agreed with the TGA. The sponsor also agreed with the conditions of registration to include the requirements listed by the quality evaluator.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Fluarix Tetra suspension for injection containing 15 µg of each of the four strains of influenza virus haemagglutinin in 0.5 mL to have an overall positive benefit-risk profile for the indication as proposed;

Fluarix Tetra is a quadrivalent vaccine indicated for active immunisation of adults and children from 3 years of age for the prevention of influenza disease caused by the influenza virus types A and B contained in the vaccine

The use of Fluarix Tetra should be based on official recommendations.

Proposed conditions of registration:

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments:

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

³¹ BS Zarvan, AJ Hibbard, G Becker. False-Positive Serologic Tests for Human T-Cell Lymphotropic Virus Type 1 Among Blood Donors Following Influenza Vaccination, 1992 MMWR Morb Mortal Weekly Rep 1993; 42(09):173-175

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Fluarix Tetra influenza virus haemagglutinin suspension for injection containing inactivated split influenza vaccine 0.5 mL pre-filled syringe, for the following indication:

Fluarix Tetra is a quadrivalent vaccine indicated for active immunisation of adults and children from 3 years of age for the prevention of influenza disease caused by the influenza virus types A and B contained in the vaccine.

The use of Fluarix Tetra should be based on official recommendations.

Specific conditions applying to these therapeutic goods

1. RMP

The Fluarix Tetra influenza virus haemagglutinin inactivated split influenza vaccine Risk Management Plan (EU RMP), version 1 dated 2 February 2012, data lock point 9 September 2011 +/- Australian-Specific Annex and any future updates, included with submission PM-2012-02287-3-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of Risk Management Plans is Routine Pharmacovigilance. Routine Pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs). Reports are to be provided annually until the period covered by such reports is not less than three years from the date of this approval letter. No fewer than three annual reports are required. The reports are to at least meet the requirements for Periodic Safety Update Reports (PSURs) as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-Periodic Safety Update Report, Part VII.B. "Structures and processes". Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

The annual submission may be made up of two Periodic Safety Update Reports each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

2. Batch Release Testing by OLSS

It is a condition of registration that all independent batches of Fluarix Tetra 1 x, 10x 15 µg/dose/strain HA 25 G needle attached and PRTC syringe imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services (OLSS).

For each batch of vaccine imported into Australia the sponsor should supply the following:

- Complete summary protocols for manufacture and QC, including all steps in production.
- Number of doses to be released in Australia from each shipment.
- Evidence of maintenance of satisfactory transport conditions between the manufacturer and Australia, such as graphs of temperature recordings, and a statement that the approved storage conditions have been met.

- At least 20 doses of each first consignment of product lot with the Australian approved labels, PI and packaging. 3 doses of any further consignment of already released product (including diluents) with the Australian approved labels, PI and packaging.
- Certificate of Release from the regulatory agency acting for the country of origin (OMCL).
- Any reagents, reference material and standards required to undertake testing, as requested by OLSS, at least 12 months prior to supply of the vaccine in Australia.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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