Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Influenza Virus Haemagglutinin H1N1, H3N2, B Victoria lineage, B Yamagata lineage

Proprietary Product Name: FluQuadri™ and FluQuadri™Junior

Sponsor: Sanofi Aventis Australia Pty Ltd

February 2015

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of common abbreviations used in this AusPAR

Abbreviation	Meaning
ACIP	Advisory Committee on Immunization Practices
AE	Adverse event
AESI	Adverse event of special interest
AR	Adverse reaction
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
GBS	Guillain-Barré syndrome
GMT	Geometric mean titer
GMTR	The ratio of the post-vaccination GMT of QIV divided by the postvaccination GMT of TIV, or the geometric mean of the individual postvaccination/pre vaccination titer ratios, as appropriate
HA	Hemagglutinin
HAI	Hemagglutination inhibition
IM	Intramuscular
PP	Per-protocol
QIV	Quadrivalent influenza vaccine
SAE	Serious adverse event
SC	Seroconversion
TIV	Trivalent influenza vaccine
US	United States
VRBPAC	Vaccines and Related Biological Products Advisory Committee

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Decision:	Approved
Date of decision:	27 November 2014
Active ingredients:	Influenza Virus Haemagglutinin H1N1, Influenza Virus Haemagglutinin H3N2, Influenza Virus Haemagglutinin B Victoria lineage, Influenza Virus Haemagglutinin B Yamagata lineage
Product names:	FluQuadri™ and FluQuadri™Junior
Sponsor's name and address:	Sanofi-Aventis Australia Pty Ltd Building D 12/24 Talavera Rd Macquarie Park NSW 2113
Dose form:	Suspension for injection
Strengths:	60 µg HA/0.5 mL dose and 30 µg HA/0.25 mL dose
Container:	Pre-filled syringe
Pack size:	10 pre-filled syringes without needle
Approved therapeutic use:	*FluQuadri and FluQuadri Junior are indicated for active immunisation of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine.* *FluQuadri is indicated for use in adults and children 3 years and older.* *FluQuadri Junior is indicated for use in children aged 6 months to 35 months inclusive.*
Route of administration:	Intramuscular (IM)
Dosage:	FluQuadri/FluQuadri Junior should be given in accordance with the national recommendation as per the current Immunisation Handbook. Administration should be carried out by the intramuscular route. The dose and schedule are detailed in the Product Information (Attachment 1)
ARTG numbers:	213963 and 213964

Product background

This AusPAR describes the application by the sponsor Sanofi Pasteur to register FluQuadri®, an egg-derived seasonal influenza vaccine containing 15 µg of each of 4

recommended influenza strains (2 A strains, 2 B strains - B/Yamagata and B/Victoria lineages, 60 µg haemagglutinin (HA) total) per 0.5 mL for the following indication:

> *FluQuadri is an inactivated quadrivalent influenza virus vaccine indicated for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine.*
>
> *FluQuadri is approved for use in persons 6 months of age and older.*
>
> *FluQuadri Junior is approved for use in children aged 6 months to 35 months requiring a 0.25 mL dose.*

The proposed indication was modified during the evaluation process to:

> *FluQuadri and FluQuadri Junior is are ~~an inactivated quadrivalent influenza virus vaccine~~ indicated for the ~~prevention~~ active immunisation of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine.*
>
> *FluQuadri is indicated for use in adults and children 3 years and older.*
>
> *FluQuadri Junior is indicated for use in children aged 6 months to 35 months inclusive.*

Influenza is an acute viral infection that circulates worldwide and spreads easily from person to person. Epidemics and outbreaks of influenza occur in different seasonal patterns, depending on the region of the world. For countries in the Southern Hemisphere, the influenza season typically begins in April and ends in September.

In Australia, 44,564 cases of laboratory-confirmed influenza were reported to the country's National Notifiable Diseases Surveillance System (NNDSS) in 2012, but wide variation existed across the territories and regions.[1]

Influenza A viruses include a number of subtypes, of which H1N1, H2N2 and H3N2 are known to have caused epidemics and pandemics. The epidemiology of influenza B is characterised by a major annual epidemic every 2 to 4 years. Since 1987, two distinct lineages of influenza B have circulated worldwide, neither providing good cross-protection against the other. The ability to predict the dominant B lineage during an influenza season has been limited. The rationale for the quadrivalent influenza vaccine (QIV) containing haemagglutinin from both circulating B lineages is to mitigate mismatches between the B lineage chosen for inclusion in the vaccine and the predominant lineage in circulation in a season, with associated potential for reduction in vaccine efficacy.

FluQuadri®/FluQuadri® Junior is a new Quadrivalent Influenza Virus (QIV) vaccine prepared from inactivated influenza viruses propagated in embryonated chicken eggs. The products are indicated for use to prevent influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine.

Regulatory status

The product is considered a new biological entity for Australian regulatory purposes.

FluQuadri, as proposed for registration in Australia, is identical to Fluzone Quadrivalent which was approved by the US FDA in 2013 (with the exception of packaging and labelling) (see Table 1 for international regulatory statusbelow). Fluzone contains 15, 9 and 60 µg HA of each strain and is prepared from influenza virus cultivated in eggs, which is inactivated with formalderhyde and disrupted with the surfactant Triton X®. Fluzone

[1]Australian Government, Department of Health. Australia's Report of the National Notifiable Diseases Surveillance System <http://www.health.gov.au>

Quadrivalent manufacture and quality control processes and facility are the same as for Fluzone. The trivalent influenza vaccine (TIV) branded Fluzone has been used in the US for over 2 decades and more than 1 billion doses have been used in the at risk population older than 6 months. Fluzone® was originally approved by the US FDA in 1947 as a whole virus vaccine, the split virus trivalent vaccine was approved in 1980.

Table 1. International regulatory status

Country	Approval date	Approved indication
USA	7 June 2013	Fluzone© Quadrivalentis indicated for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine and is approved for use in persons 6 months of age and older.
Canada	6 February 2014	Same as in the USA.

Fluzone has not been registered in Australia, however Sanofi has marketed a TIV vaccine under the trade name Vaxigrip (AUST R 80198) and Vaxigrip Junior®. Dependent on seasonal requirements this product has included the same 2 Type A viruses in combination with one of the same 2 Type B viruses included in Fluzone but is sourced from a different manufacturing site and has undergone a separate development program to establish quality, safety and immunogenicity attributes.

An application for registration of inactivated quadrivalent influenza vaccine (split virion) has also been submitted to New Zealand and is currently pending in this jurisdiction.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Drug substance (active ingredient)

This substance is manufactured using conventional egg inoculation, harvest, inactivation and purification procedures. The virus is inoculated in embryonated hen's eggs, incubated, purified by zonal centrifugation on a sucrose gradient. The concentrated zonal pool is split using Triton-X-100 to disrupt virus particles prior to inactivation with formalydehyde. Inactivation conditions are strain specific. The inactivated, split virus concentrate is diafiltered and volume adjusted to meet the target haemagglutinin (HA) concentration. The drug substances, monovalent concentrates of the sample strain may be pooled.

The virus seed lot system including pre-master, master and working seeds have been described. Seed lots have been characterised in terms of sterility, phenotypic and genotypic analysis.

All viral/prion safety issues have been addressed.

Specifications

The following Release testing is conducted on the drug substance: sterility, virus inactivation, potency via single radial immunodiffusion (SRID) formaldehyde, endotoxin, identity and pH. The company have now included assays for neuraminidase and splitting as stated in the European Pharmacopiea (EP) monograph 0158 for influenza, (split virion, inactivated).

Appropriate validation data have been submitted in support of the test procedures. Issues surrounding the potential for the overestimation of HA content due to antisera cross-reactivity when testing bivalent bulks with bivalent B references have been addressed by the sponsor in consultation with the TGA.

Stability

Stability data have been generated under real time and accelerated conditions.

Drug product

The drug product is formulated by combining the four monovalent concentrates and diluting with phosphate buffered saline (PBS). The quantity of each monovalent is dependent on the HA concentration. The final product HA concentration is 30 µgHA/mL. The drug product is supplied in either 0.5 mL or 0.25 mL single dose pre-filled syringes in packs of 10, without needles.

The product is formulated by combining the 4 strains and PBS to 60 µg HA/0.5 mL or 30 µgHA/0.25 mL.

Specifications

The sponsor has agreed to perform SRID and Endotoxin on the Final Container. Appropriate validation data have been submitted in support of the test procedures.

Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. The company has agreed to establish minimum target formulations at the start of each season for H1 and H3 strains that enable the product to comply with potency specification through the shelf life. The proposed shelf life is 12 months when stored at 2 to 8°C. The product should be shaken before use. *Do not freeze* is stated on the outer packaging.

Quality summary and conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological and biopharmaceutic data (as applicable) 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.

Issues of concern

A number of deficiencies and other issues requiring resolution before the product can be recommended for approval were identified during the evaluation and have been referred to the applicant for comment or resolution. The sponsor has responded to the issues raised and the responses have been evaluated.

Quality recommendation

The quality evaluator recommend that for FluQuadri and FluQuadri™Junior 60 µg HA/0.5 mL dose and 30 µg HA/0.25 mL dose, prefilled syringe without needle with a shelf life of 12 months at 2 to 8C should be approved. The sponsor has agreed to provide target formulation values to the TGA prior to the commencement of each season.

The quality evaluator recommended the following condition of registration:

Batch release testing by the TGA

It is a condition of registration that all independent batches of FluQuadri FluQuadri and FluQuadri™Junior 60 µg HA/0.5 mL dose and 30 µg HA/0.25 mL dose, prefilled syringe without needle 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. 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.

III. Nonclinical findings

Nonclinical summary

The sponsor provided adequate justification for the lack of nonclinical studies for FluQuadri® in the Nonclinical Overview, on the basis of clinical data for the vaccine, and extensive marketing experience with the related vaccines. Reference was made to 2 local tolerance studies and a developmental and reproductive toxicity study conducted with Fluzone ID®, which were not submitted, but are reviewed on the FDA website, and raise no registration issues:

> *"In the reproductive and developmental toxicity study, rabbits received either saline or one human dose of Fluzone Intradermal twice before mating and on gestation day 6 and 27, or Fluzone Intradermal twice before mating and on gestation day 12 and 27. Rabbits then either underwent Caesarean section on day 29 post-coitum and were submitted for embryotoxicity evaluations, or were allowed to litter. There were no treatment-related effects on the reproductive performance, no test-article-related-effects in terms of the pre- and post-implantation data, fetal weight or sex (no association was found between vaccine treatment and incidences of soft tissue and skeletal anomalies and their variations), and no test article-effects were reported on pup survival (from birth to weaning), pup weight, pup sex or physical development. Based on these data, intradermal administration of Fluzone Intradermal containing 27 µg HA per dose did not produce any maternal or developmental toxicity in ---------(b)(4)-------- rabbits.*
>
> *In one local toxicity study, female ---------(b)(4)-------- rabbits received one human dose of Fluzone Intradermal on study day 0, 14 and 28 intradermally or of Fluzone intramuscularly on day 0 followed by an intradermal injection of one human dose of Fluzone Intradermal on study day 14 and 28, with each injection administered at a unique site. On study days 31 and 42, a necropsy was performed and the histopathology of the injection site was evaluated. Injection-site reaction in vaccinated animals consisted of mild to moderate dermal inflammation with mixed cell infiltration which was of reduced severity and frequency after the recovery phase. Animals receiving Fluzone Intradermal showed mild erythema and edema, and minimal induration. In the second local toxicity study, female ---------(b)(4)-------- rabbits received Fluzone Intradermal at a dose of either 21 or 15 µg HA/strain on study days 0, 14 and 27 or 15µg HA/strain of Fluzone on study day 0 intramuscularly followed by 21µg HA/strain Fluzone Intradermal on study days 14 and 27, with each injection administered at a unique site. On study days 30 and 41, a*

necropsy was performed and the histopathology of the injection site was evaluated. Injection-site reaction consisted of moderate to marked dermal inflammation with mixed cell infiltration which was of reduced severity and frequency after the recovery phase. Animals showed a moderate to marked edema, mild erythema and minimal induration; all Draize scores returned to baseline before the end of the recovery phase."

Fluzone QIV® was approved in June 2013 in the USA and no nonclinical data were submitted to the FDA.

Nonclinical recommendation

There are no nonclinical objections to registration of FluQuadri® and FluQuadri Junior®.

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

Clinical rationale

FluQuadri is identical to Fluzone Quadrivalent approved by the FDA on 7 June 2013. Fluzone QIV manufacture is based on the same process as Fluzone High-Dose. The only difference between Fluzone and Fluzone Quadrivalent relates to an increase in HA content to a total target of 60 µg, based on 15 µg/strain. Fluzone and Fluzone Quadrivalent are manufactured in the United States.

As the same manufacturing process applied for concentrates of Fluzone Quadrivalent and Fluzone, the Center for Biologics Evaluation and Research (CBER) advised that validation of the QIV final bulk formulation and mixing processes, including stability studies on consistency lots would be sufficient for US licensure of the QIV manufacturing process, and a clinical endpoint lot consistency study would not be required. Sanofi Pasteur stated that it does not consider it pertinent to provide a comparison of manufacturing in relation to Sanofi Pasteur's influenza vaccines, FluQuadri/Fluzone and Vaxigrip.

Fluzone is not registered in Australia. The supply to Australia has been from the French site manufacturing the TIV Vaxigrip which underwent a separate development program for registration. It has been registered for use in Australia for 27 years with more that 17 million doses administered.

Sanofi Pasteur's development of the quadrivalent vaccine is based on the following rationale. In Australia, minor or major epidemics of type A or type B influenza occur most years, usually during the winter. In 2012, 44,564 cases of laboratory confirmed influenza were reported to the country's National Notifiable Diseases Surveillance System. It is estimated that influenza causes 3,500 deaths, about 18,000 hospitalisations, and 300,000 GP consultations each year. The highest influenza burden is seen in the elderly and in children less than 5 years of age.

Influenza A viruses include a number of subtypes, of which H1N1, H2N2 and H3N2 are known to have caused epidemics and pandemics. The epidemiology of influenza B is characterised by a major annual epidemic every 2 to 4 years. The burden of disease from influenza B is generally less than H3N2 but greater than H1N1.

Since 1987, two distinct lineages of influenza B have circulated worldwide, neither providing good cross-protection against the other. The ability to predict the dominant B

lineage during an influenza season has been limited, resulting in mismatches between the lineage chosen for inclusion in the vaccine and the predominant lineage in circulation.

Data presented by World Health Organization (WHO) Collaborating Centre for Reference and Research on Influenza, indicates all four strains of influenza virus represented in the quadrivalent vaccine are implicated in the influenza-related morbidity observed in Australia. B strains were responsible for more than 20% of cases of influenza reported in Australia in 2004 to 2006 and 2011 to 2012 and more than 60% in 2008.

The effectiveness of the influenza vaccine in preventing or attenuating influenza illness depends in part on the age and immune competence of the recipient and on the similarity between the virus strains present in the vaccine and those circulating in the community. With a good match between vaccine and circulating strains, influenza vaccine has been shown to prevent illness in 70% to 90% of healthy individuals aged less than 65 years, and to be 30% to 70% effective in preventing hospitalization among community-based elderly. Among the elderly in nursing homes, influenza vaccine may be only 30% to 40% efficacious in preventing influenza disease but can be 50% to 60% effective in preventing hospitalization and pneumonia and 80% effective in preventing death.

During the Vaccines and Related Biological Products Advisory Committee meeting 2009, the Centers for Disease Control and Prevention (CDC) presented a model to assess the potential impact on the number of influenza cases, hospitalizations, and deaths of a quadrivalent vaccine compared with trivalent vaccine. Their model included 10 influenza seasons (1999 to 2000 to 2008 to 2009). The proportion of all influenza disease identified as type B varied from 0.4% to 46%. The proportion of type B isolates of a lineage not in a given year's TIV varied from 0% to 98%. Over the 10 seasons, it was estimated that a quadrivalent vaccine would have reduced the burden of influenza disease in the US by 2.7 million cases, 21,440 hospitalizations and 1371 deaths.

Justification for bridging results from the submitted studies, to children 9 to 17 years of age is based on CBER guidance that the safety and immunogenicity of QIV could be inferred from the safety profiles of QIV in children 6 months to < 9 years of age and in adults 18 years of age and older.

Contents of the clinical dossier

Three pivotal clinical studies of safety and immunogenicity were provided:

- Study GRC43 was a Phase II, randomised, open-label, controlled, multi-centre clinical trial including adults 18 years of age and older, in which antibody responses to the quadrivalent influenza vaccine (QIV) were compared with those of 2009 to 10 TIV and 2008 to 09 TIV
- Study QIV03 was a Phase III, randomised, active-controlled, multi-centre clinical trial including participants aged 65 years and over. Antibody responses to QIV were compared with those of 2010 to 2011 TIV and an investigational TIV containing the alternate B/strain
- Study QIV04 was a Phase III, randomised, observer-blinded, active-controlled, multi-centre clinical trial in children from 6 months to less than 9 years of in which antibody responses and safety of QIV were compared with results for of 2010 to 11 TIV and an investigational TIV.

Good clinical practice

The following assurances were given.

Study GRC43 – adults ≥ 18 years

The final protocol, version 4.0, under which all participants were enrolled, was approved by the Institutional Review Board (IRB) of Duke University Health System, Chesapeake Research Review, and Quorum Review.

The trial was conducted in accordance with the South African version of the Declaration of Helsinki, and International Conference on Harmonization (ICH) Good Clinical Practice, applicable national and local requirements regarding ethical committee review, informed consent, and other statutes or regulations on the protection of rights and welfare of participants in biomedical research.

Informed consent forms contained core information but may have differed by centre depending on local regulations and IRB requirements. If the participant was unable to read and sign, informed consent form was signed and dated by an impartial witness.

Study QIV03 – adults ≥ 65 years

The original trial protocol used for this trial, version 1.0 (dated 02 August 2010), was approved by the Quorum Review IRB prior to the start of the trial. One protocol amendment, 13 October 2010, was issued during the trial. Participants were enrolled under protocol versions 1.0 and 2.0.

This trial was conducted in accordance with the Edinburgh revision of the Declaration of Helsinki, Good Clinical Practice, the ICH guidelines, the applicable national and local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human participants participating in biomedical research

Study QIV04 – children 6 months to < 9 years

There were 4 protocol amendments: 03 August 2010; 07 October 2010; 20 October 2010; 28 February 2011 and final version 5.0 dated 08 July 2011. Enrolment commenced under version 3.0. Protocol versions 2.0 to 5.0 were approved by the Quorum IRB. All trial related documents and any amendments were approved by the investigational sites' IRBs.

The trial was conducted in accordance with the revision of the Declaration of Helsinki, Good Clinical Practice, ICH guidelines, applicable national and local requirements, and other statutes or regulations regarding the protection of the rights and welfare of participants in biomedical research.

Written informed consent obtained before any study procedures were performed was signed by the child's representative. Children 7 years of age or older, based on IRB specifications, may have been asked to review and sign a study assent form.

Pharmacokinetics

No new data submitted.

Pharmacodynamics

No new data submitted.

Dosage selection for the pivotal studies

No new data submitted.

Efficacy

Clinical immunogenicity

The three submitted studies have been presented separately in this clinical evaluation (see Attachment 2) due to differences in study design. The following features were common to the three studies:

- In each of the studies, assessment of immunogenicity was the primary objective
- No efficacy data was presented
- Serum antibody responses to the influenza viruses were considered to correlate with protection against infection and serve as valid surrogates of vaccine efficacy
- The method used to measure serum antibodies in the clinical studies was the haemagglutination inhibition (HAI) test.

Assessment of immunogenicity post vaccination was uniform amongst the studies:

- Seroprotection was defined as an HAI antibody titre ≥ 40 (l/dil) at pre and postvaccination
- Seroconversion was defined as a pre-vaccination titre < 10 (1/dil) and a postvaccination titre ≥ 40 (1/dil), or a pre vaccination titre ≥ 10 (1/dil) and a ≥ 4 fold increase in postvaccination titre
- Geometric mean titre ratio (GMTR) was calculated postvaccination (Geometric Mean Titre (GMT) QIV/ GMT TIV).

Missing or incomplete immunogenicity data were not replaced and there was no search for outliers. If there were two or more titres, the geometric mean was calculated and was used in the calculation of primary and observational immunogenicity endpoints. Missing safety data was not replaced.

Any antibody titre reported as < lower limit of quantitation (LLOQ) was converted to a value of 0.5 LLOQ to calculate the GMTs. When fold rise was calculated, pre vaccination values reported as < LLOQ were converted to LLOQ; postvaccination titres reported as < LLOQ were reported as 0. If both pre and post values were < LLOQ, the fold rise was defined as 1.

Evaluator's conclusions on immunogenicity

Study GRC43

The evaluator is not in a position to comment on similarity or otherwise of the results presented in this submission and the initial testing submitted to CBER.

The primary objective was met in protocol defined terms and the vaccine would have passed the criteria necessary for registration as a seasonal vaccine based on relevant European Union (EU) guideline criteria.[2]

Because the description of the study vaccine included gelatine and there is no mention of animal products in the application form or in the proposed Product Information, it is unclear whether the prototype vaccine manufacture was exactly the same as the vaccine proposed for registration in Australia.

[2]CPMP/BWP/214/96 Note for Guidance on Harmonization of Requirements for Influenza Vaccines.

Study QIV03

The applicant's reasoning regarding failure to meet the criteria for non-inferiority of seroconversion rate to A/H1N1 and superiority of GMT ratio for B/Brisbane are accepted. However, the findings are in keeping with the previously well documented muted antibody responses to influenza vaccination in the elderly, and without direct evidence of efficacy, translation of the results into predictions of efficacy is hypothetical.

There was no protocol defined yardstick for evaluation of GMTs, GMT ratios (GMTRs), seroconversion and seroprotection rates. However, the guideline Committee for Proprietary Medicinal Products (CPMP)/Biotechnology Working Party (BWP)/214/96[2] was current at the time of this study and is considered relevant to the Australian setting. Applying the CPMP criteria, each vaccine met each criterion in response to A/California and A/Victoria. Antibody responses to B/strains were less vigorous than to A/strains. According to the Guideline, the geometric mean increase criterion was met the QIV but by neither of the TIVs. No vaccine passed the seroconversion criterion. Each of the vaccines passed the seroprotection criterion including the vaccine that did not contain B/Brisbane.

Results for B/Florida were better for the QIV than the TIVs. According to CPMP criteria, the QIV and the TIV containing the relevant antigen just passed all three criteria while the TIV without B/Florida passed none of the criteria.

Study QIV04

Reverse cumulative curves illustrate that the participants in both age strata and overall had a greater response to the A strains than the B strains. Children aged 3 to < 9 years had greater responses to all antigens than those aged 6 months to < 36 months. Those children who received two doses had greater response than those who received one dose. The age range of those who received 2 doses is uncertain. An efficacy study would be ideal especially for the youngest children.

It is accepted that the antibody response appears at least as good for the quadrivalent vaccine as the trivalent vaccine.

Safety

Studies providing safety data

Two adult studies GRC43 and QIV03 and one paediatric study QIV04 were provided.

Assessment of safety was an observational objective in each of three studies. No hypothesis was tested. Missing data was not replaced. Unless otherwise specified, in the account of safety in this report, percentages were for participants per group, not events.

Evaluator's conclusions on safety

The following is a summary from the sponsor's submission:

> *In the adults studies, the safety profile for QIV was similar to the currently licensed 2010-2011 TIV vaccine Fluzone and the investigational TIV. No safety concerns were identified.*
>
> *In the paediatric study, solicited injection site and systemic reactions, unsolicited AEs[3], and SAEs[4] were reported at similar rates between the QIV group and the 2 control TIV groups. The safety data from study QIV04 did not raise any safety*

[3] AEs=adverse events
[4] SAE=serious adverse events

concerns for QIV. Overall, the safety data demonstrated that the addition of the alternate-lineage B strain to existing TIV did not alter the reactogenicity and tolerability profiles of the vaccine. It was reassuring that rates of fever and febrile seizures were not higher among children administered QIV compared with those among children administered the control TIVs.

The evaluator stated that the findings, as presented in the dossier, accord with the applicant's conclusion.

Clinical questions

Question 1

Are the vaccines used in Studies GRC43, QIV03 and QIV04 exactly the same as the vaccine proposed for registration? The description of QIV in the three submitted studies includes mention of gelatine. The draft product information does not mention gelatine, submission states that the product does not contain gelatine and the Application Form states that there is no component of animal origin.

Question 2

Explanation has briefly been given as to why lot-to-lot consistency study was not required by CBER. Explanation as to why such study would not be required for Australian purposes is requested, given that Fluzone is not registered in Australia.

Question 3

In each of the studies, no justification for choice of the non-inferiority and superiority margins could be located. Please provide a justification.

Question 4

In Study QIV04 protocol version 5, the observational safety objectives included collection and analysis of clinical information on the number of all-cause hospitalizations, emergency room visits, and unscheduled physician visits during the 6 months following the final vaccination. Information regarding the incidence of influenza and influenza like illness in participants who sought medical help in the 6 months following vaccination is of interest.

The following statement was included in the submission in a footnote: "*The observational objectives for Studies QIV03 and QIV04 incorrectly stated that Sanofi Pasteur would descriptively analyze hospitalizations, emergency room visits, and unscheduled physician visits. Rather, hospitalizations, emergency room visits, and unscheduled physician visits were collected and analyzed as unsolicited AEs, AESIs, and SAEs*"

Reports of Influenza like illness and influenza are spread throughout numerous tables. It was difficult to get an overall picture of the incidence of these from the multiple locations. Please collate and present the incidences between Visit 1 and end of 6 month follow-up and timing in relation to vaccination. If possible, report the strain of influenza virus causing illness.

Question 5

Please explain why the proposed tradename is FluQuadri rather than Fluzone Quadrivalent. In a mobile world, standard naming is considered to be preferable.

Question 6

Currently The Australian Immunisation Schedule recommends influenza vaccination for infants from 6 months of age. Please provide information on the numbers of infants aged between 3 and 6 months included in QIV04, the immunogenicity as safety results and adverse event profiles in that age range.

Question 7

Please justify the statement in the Product Information: "*If GBS has occurred within 6 weeks of previous influenza vaccination, the decision to give FluQuadri/FluQuadri Junior should be based on careful consideration of the potential benefits and risks*."

Question 8

The applicant was requested to respond to the evaluator's comments on the Product Information (the details of which is beyond the scope of this AusPAR).

Question 9

Sanofi Pasteur was requested to respond to the evaluator's comment on the proposed Consumer Medicine Information (CMI) (the details of which is beyond the scope of this AusPAR).

For details of the sponsor's responses and the evaluator's comments on the sponsor's responses see Attachment 2 of this AusPAR.

Clinical benefit-risk assessment

Sanofi Pasteur's quadrivalent vaccine is an extension of the trivalent influenza vaccine, Fluzone, which is manufactured and licensed in the US. Antigen production for the quadrivalent vaccine is the same as the manufacturing process for Fluzone trivalent influenza vaccines.

In essence the development rationale was that, while annual influenza vaccination is the most effective method of prevention of influenza to date, the current influenza vaccination schedule includes only one of the two influenza B phylogenetic lineages with resultant risk of mismatch with the dominant circulating B strain. Modelling suggests that inclusion of two B/strains may reduce mortality and morbidity due to influenza caused by the B/strain not included in the seasonal trivalent vaccine.

In support of the application, three active-controlled, randomised studies undertaken in the USA were supplied. GRC43 a Phase II open-label study included adults ≥ 18 years, QIV03 and QIV, Phase III partially blind studies, included respectively, adults ≥ 65 years and children from 3 months to < 9 years.

The applicant argued that immunogenicity of QIV could be inferred from demonstration of the safety and immunogenicity profiles of QIV in children 6 months to < 9 years of age and in adults 18 years of age and older. This is accepted.

The objectives of the three studies are summarised below. With regard to immunogencity, there was a consistent approach to definition, measurement of antibodies and statistical analysis between studies.

Table 3. Objectives of the three studies submitted.

	Study GRC43	Study QIV03	Study QIV04
Non-inferiority GMT	Primary (B/strains assessed)	Primary (A and B strains)	Primary (A and B strains)
Non-inferiority seroconversion	N/A	Observational	Primary
Superiority GMT	N/A	Observational	Secondary
Superiority Seroconversion	N/A	Observational	Secondary
Antibody Responses	Observational	Observational	Observational
CPMP criteria	Observational	N/A	N/A
Safety	Observational	Observational	Observational

Study GRC43

The participants aged ≥ 18 years were randomised to one of three groups of 190 and received one 0.5 mL intramuscular dose of vaccine as follows:

Group 1	2009-2010 licensed TIV
Group 2	2008-2009 licensed TIV
Group 3	Candidate quadrivalent

The per-protocol population included between 98.4 to 100% of randomised participants. Demographics were evenly spread. Mean ages were 55.0 to 56.7 years. Females accounted for approximately two thirds; Caucasian accounted for 87.4%; to 91.1%.

The primary objective was met. Non-inferiority in terms of GMT was shown for both B strains. The quadrivalent vaccine met each of the 3 CPMP criteria for each age group. A generally greater antibody response to vaccination was reported in individuals 18 to 60 years of age compared to those age ≥ 61 years.

There were no unexpected safety findings and no new safety signal detected. There were no reports of immediate reactions, serious adverse reactions including deaths, no events of special interest and no discontinuations occurred. Solicited injection site reactions and systemic reactions were no more common in the QIV group than in the TIV groups. Grade 3 solicited symptoms and non-serious Grade 3 unsolicited adverse reactions were infrequent in all groups.

Study QIV03

Participants aged ≥ 65 years were randomised to one of three groups of 225 and received one intramuscular dose of assigned vaccine as follows:

Group 1	Quadrivalent vaccine
Group 2	Investigational TIV with alternate B/strain
Group 3	2010 – 2011 licensed TIV

The per-protocol population included between 97.3 to 98.2% of randomised participants. Demographics were similar across groups, the mean age of the three groups was approximately 72 years, approximately 90% were Caucasian.

The primary objective was met. Non-inferiority in terms of GMT was shown for all four strains. Observational objectives, non-inferiority in terms of seroconversion and superiority in terms of GMT and seroconversion were met with the exception of superiority of QIV GMTR for B/Brisbane.

Pre vaccination GMTs were measurable for each strain with increase in antibody levels postvaccination for all four virus strains. Responses for B strains were at lower levels than for A strains.

There was no protocol defined yardstick for evaluation of antibody responses. The guideline[2], which has been adopted in Australia, was current at the time of this study and is considered relevant to the Australian setting. Assessment against this guideline criterion is as follows:

- A/California: Each vaccine passed each criterion
- A/Victoria: Each vaccine passed each criterion
- B/Florida: The QIV and the TIV containing the relevant antigen just passed all three criteria while the TIV without B/Florida passed none of the criteria
- B/Brisbane: The geometric mean increase criterion was passed by QIV but by neither of the TIV vaccines. No vaccine passed the seroconversion criterion. Each of the vaccines passed the seroprotection criterion including the vaccine which did not contain B/Brisbane.

No unexpected safety findings were reported and there was no new safety signal reported. No serious adverse event was considered vaccine related. There were no reports of death, no reports of adverse events of special interest or no immediate reactions were reported. Solicited injection site reactions were more common in the QIV group; incidences of solicited systemic reactions were similar for QIV and the 2010 to 2011 TIV group. Grade 3 solicited and unsolicited reactions were infrequent.

Study QIV04

Participants were randomised to one of three groups as shown below. Enrolment was stratified by age: 3 to < 36 months and 3 to < 9 years of age.

Group 1	2010 – 2011 TIV	N = 800
Group 2	Investigational TIV	N = 800
Group 3	QIV	N = 3340

In total 4363 were randomized; 15 (0.3%) were randomized but not vaccinated; 4013 (92.0%) completed the study. The per-protocol population included 80.6% in the QIV group, 79.1% in the 2010 to 2011 TIV group, and 82.6% in the investigational TIV.

Demographic characteristics were evenly spread. A total of 2210 males and 2153 females enrolled. The mean ages were between 49.6 and 49.8 months. The majority were Caucasian QIV, 58.3%; 2010-2011 TIV, 58.8%; investigational TIV, 57.5%, or Black 20.5%; 2010-2011 TIV 20.0%; investigational TIV 19.2%.

The primary objectives were met. Non-inferiority of QIV GMTs and seroconversion rates was shown for each strain for each age group and overall. The secondary objectives were met. Superiority of QIV was shown for each strain overall and for both age groups for post-vaccination GMTs and seroconversion rates.

Pre-vaccination GMTs were measurable for each strain with increase in antibody levels demonstrated for all four virus strains post-vaccination. Children in both age strata had a greater response to the A strains than the B strains. Children aged 3 to < 9 years had greater responses to all antigens than those aged 6 months to < 36 months. Those children who received two doses had greater response than those who received one dose.

As with Study QIV03, there was no protocol defined measure for assessment of responses. According to CPMP/BWP/214/96[2], there are no criteria for children; however, the results are discussed here in relation to adult criteria.

6 months to < 9 years:

- A/California: All adult criteria met by each vaccine
- A/Victoria: All adult criteria met by each vaccine
- B/Brisbane: All adult criteria met by QIV and TIV (Brisbane), no criteria met by TIV (Florida)
- B/Florida: All adult criteria met by QIV, GMTR and seroconversion adult criteria met by TIV (Florida) and seroprotection rate elderly criterion met by TIV (Florida) No criteria met by TIV (Brisbane).

6 to < 36 months:

- A/California: These results passed as the criteria 18 to 60 year old adults
- A/Victoria: These results passed all the criteria for 18 to 60 year old adults
- B/Brisbane: All criteria passed by QIV for adults for QIV and none were passed for the TIV not including B/Brisbane. The TIV containing B/Brisbane passed the adult criteria for GMTR and seroconversion rate and passed the elderly criterion for seroprotection
- B/Florida: QIV and TIV (Florida) passed GMTR and seroconversion criteria. The seroprotection criteria for adults and the elderly were failed by all three vaccines.

Results for B/Florida over all age strata were also borderline appearing to be attributable to the results for the youngest participants. However, results for QIV were if anything marginally better than those for TIVs.

3 to < 9 years:

- A/California: Result met all adult criteria
- A/Victoria: Results met all adult criteria
- B/Brisbane: All adult criteria were met for QIV, GMTR and seroprotection criteria were met by TIV (Brisbane), GMTR elderly criterion was met by TIV (Florida). The seroprotection criterion for both adults and the elderly was not met by TIV (Florida)

- B/Florida: All adult criteria were met by QIV and TIV (Florida). TIV (Brisbane) met elderly criterion for GMTR, but failed both seroconversion and seroprotection criteria for adults and the elderly.

One dose:

- A/California: All adult criteria met by each vaccine
- A/Victoria: All adult criteria met by each vaccine
- B/Brisbane: QIV vaccine met 2 adult criteria, GMTR and seroconversion and passed elderly criterion for seroprotection. TIV (Brisbane) passed GMTR and seroconversion adult criteria and elderly criterion for seroprotection. TIV (Florida) passed none of the criteria
- B/Florida: Both QIV and TIV (Florida) passed adult criteria for GMTR and seroconversion and passed elderly criteria for seroprotection. TIV (Brisbane) passed none of the criteria.

Two doses - all ages:

- A/California: All adult criteria passed for each vaccine
- A/Victoria: all adult criteria passed for each vaccine
- B/Brisbane: All adult criteria passed for QIV and TIV (Brisbane). TIV (Florida) failed all three criteria
- B/Florida: QIV passed all adult criteria, TIV (Florida) passed adult criteria for GMTR and seroconversion rate and passed elderly criterion for seroprotection. TIV (Brisbane) passed none of the criteria.

In relation to the safety objective, there were no unexpected safety findings and the safety profile of the quadrivalent vaccine was similar to that of the trivalent vaccines.

- Immediate reactions were documented in 0.6% of participants in each group
- Solicited local reactions were more common in the QIV group than the TIV groups for children aged 3 to < 36 months; however significance of this was not tested. Otherwise there was no consistent difference apparent in solicited symptoms reported. Grade 3 reactions solicited local reactions were reported by < 2% of each group. Grade 3 solicited systemic reactions were reported by similar percentages of participants in the QIV and investigational TIV groups
- Unsolicited adverse reactions were reported by similar percentages
- Discontinuation due to adverse event was reported for 0.3% of the QIV group, 1% or the 2010 to 2011 TIV group and 0% of the investigational TIV group
- A serious adverse event considered vaccine related within the 6-month follow-up period was reported for 1 child in the QIV group (croup) and one in the investigational TIV group (febrile convulsion). There were none reported in the 2010-2011 TIV group
- One death (drowning) was unrelated to vaccination
- Febrile convulsions were the only events of special interest reported. There were 14 reports of febrile seizures involving 13 participants (8 in the QIV group, 2 for the 2010-2011 TIV group and 3 in the investigational TIV group). Two occurred within 24 hours of vaccination and were considered vaccine related: one child vaccinated with the 2010 – 2011 TIV one with the investigational TIV.

The only change to the conduct of the study considered to have possible impact on study objectives was included in protocol version 4 relating to use of 0.5 mL prefilled single vials rather than 0.25 mL prefilled syringes for use in children 6 months to < 36 months, which

resulted in reliance on staff accuracy in measurement and thus had the potential to impact the results of the study.

Assessment of safety in the youngest children was complicated by developmental language difficulty. Subjective assessment of adverse events for very young children can be difficult particularly for the youngest children.

Conclusion

The immunogenicity and safety results of the three studies support the application. Efficacy is inferred; however, future study of efficacy is recommended.

Risk benefit assessment

Benefits

Influenza is a highly contagious, acute viral respiratory disease with epidemic potential, affecting all age groups but with particular risk for complications including death in the very young, older adults and individuals with underlying health problems. Influenza may also extract an economic toll due to time lost from work and increased use of medical facilities.

To date, vaccination has proven the most effective form of prevention against influenza. Theoretically, inclusion of two B/strains may increase vaccine efficacy and reduce the potential for mismatch between vaccine and circulating B strains.

Sanofi Pasteur's trivalent influenza vaccine, Fluzone, manufactured similarly to the candidate QIV, has long a long history of safe use in the USA.

The reported adverse reactions were predominantly of low grade severity and short duration. The safety profile of QIV reported in the three submitted studies was similar to that of the trivalent comparators. No new safety signal was reported.

Risks

Adverse reactions were common. The numbers, by age strata included in the studies may have been too small to fully determine the safety profile of QIV with respect to rare events.

The antibody response to B/strains appeared considerably less than that for A/strains and response to each was less for children < 3 years of age and for adults ≥ 65 years of age, that is, those at greatest risk of influenza morbidity and mortality. Efficacy for B/strains remains to be tested. There is a risk that the added antigen will not result in increased efficacy in these individuals.

The price of the quadrivalent vaccine to the consumer in comparison to the trivalent vaccine is unknown. Added cost would be required to be offset by added efficacy.

Balance

The balance is considered to lie on the side of potential benefit.

Clinical recommendation

Registration of FluQuadri is recommended for the indication proposed.

An efficacy study is recommended with particular attention to efficacy in children less than 3 years of age and adults ≥ 65 years of age.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted an Australian Risk Management Plan (AUS-RMP) Version: 1.0 with an Australian-Specific Annex version 1.0 (v 1.0) (March 2013) which was reviewed by the TGA's Office of Product Review (OPR).

This AUS-RMP (v1.0) is derived from the Core RMP v 1.0 (using a Data Lock Point (DLP) of 15 March 2013) and comprises the following documentation:

- Core RMP v 1.0
- Australian Specific Annex (ASA) v 1.0

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 4.

Table 4. Sponsor's summary of Ongoing Safety Concerns

Important identified risks	None
Important potential risks	Adverse events of special interest: • Thrombocytopenia • Anaphylaxis • Guillain-Barré syndrome • Convulsions (including febrile) • Neuritis (including Bell's palsy) • Encephalitis/myelitis • Vasculitis
Important missing information	Very rare unanticipated adverse events that could not be identified during the clinical development program At the time of this Risk Management Plan (RMP) version, Fluzone Quadrivalent vaccine has not been systematically studied in: • Pregnant or lactating women • Immunocompromised patients • Patients with chronic debilitating diseases, chronic cardiac, pulmonary, renal and metabolic disorders (e.g., diabetes), at risk of developing severe influenza and complications of acute infection Vaccine efficacy/effectiveness

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities to monitor all specified ongoing safety concerns.

Below is the table of on-going and planned additional Pharmacovigilance studies/activities in the Pharmacovigilance Plan.

Table 5. On-going and planned studies in the Post-authorization Pharmacovigilance Development Plan

Study/activity	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
Postmarketing Commitment to Conduct Pregnancy Exposure Registry	Observational for pregnancy outcomes and Infant outcomes	Not applicable	Pending initial approval and protocol approval	Yearly interim reports in PBRER and likely final report December 2020

Risk minimisation activities

The ASA provides details of the local pharmacovigilance organisation and risk minimization activities. Routine risk minimisation activities are proposed for all safety concerns except the important missing information.

The table below summarises the sponsor's conclusion in regard to the need for risk minimisation activities.

Table 6. Planned actions for the evaluation of the need for risk minimisation activities

Safety concerns		Type of risk minimisation activity
Important identified risk	None	Not applicable
Important potential risks	Thrombocytopenia	Routine
	Anaphylaxis	Routine
	Guillain-Barré syndrome	Routine
	Convulsions (including febrile)	Routine
	Neuritis (including Bell's palsy)	Routine
	Encephalitis/myelitis	Routine
	Vasculitis	Routine
Important missing information	Pregnant or lactating women	None
	Immunocompromised patients	None
	Patients with chronic debilitating diseases, chronic cardiac, pulmonary, renal and metabolic disorders (e.g., diabetes), at risk of developing severe influenza	None
	Vaccine efficacy/effectiveness	None

Reconciliation of issues outlined in the RMP report

Table 7 summarises the OPR's first round 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 7. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated request and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	*The sponsor confirms that the Nonclinical and Clinical Evaluation Reports have been reviewed to ensure that the any safety considerations raised have been considered for relevance to the Risk Management Plan and addressed accordingly.*	This is acceptable.
The reason for not calling the vaccine Fluzone Quadrivalent (as in USA) is not clear. The sponsor is requested to clarify the reason behind not proposing a standard name for the vaccine.	*Fluzone Quadrivalent was initially licensed in the United States but Sanofi Pasteur is now expanding licensure to several countries in the northern and southern hemispheres.* *Several health authorities in southern hemisphere countries objected to the use of the trade name "Fluzone"; therefore, Sanofi Pasteur researched the use of another trade name.* *Since the majority of countries that will license quadrivalent influenza vaccine (QIV) are expected to use the name FluQuadri, Sanofi Pasteur proposes to continue to use the*	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	name FluQuadri for QIV in Australia, unless there is a more compelling scientific or medical rationale to change.	
The proposed wording in the indication might lead to incorrect administration of the vaccine. The risks are presented below; There is potential risk of administration of the whole 0.5 ml in children aged 6 months to 35 months at one time, There is potential risk of incorrect preparation, measurement and storage of the half dose, There is potential risk that the vaccine might be used in sequential patients. It is recommended that the risks mentioned above are addressed in the RMP.	The sponsor has proposed a revised indication in their response as follows: *FluQuadri is indicated for use in adults and children 3 years and older.* *FluQuadri Junior is indicated for use in children aged 6 months to 35 months inclusive.* Additionally the sponsor has provided the following comments: *… clear instructions regarding the preparation, administration, and storage of the vaccine (which is only supplied in a single-dose syringe presentation) are provided in the proposed PI. Accordingly, it is not considered necessary to include further measures to address the above risks in the RMP.*	The evaluator notes the revised indication for final consideration by the Delegate.
It is recommended that the Delegate may wish to replace "Immunisation Handbook" with "Australian Immunisation Handbook" in the proposed "Dose and administration" Section.	*The sponsor proposes to keep the wording more general in nature as the overall intention for this labelling is that it will be applicable in both Australia as well as New Zealand.*	This recommendation is for final consideration by the Delegate.
It is recommended that the following be added to the list of ongoing safety concerns,	The sponsor has provided a justification for not including the	The sponsor's response is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
unless the sponsor can provide compelling justification for their exclusion: Long term safety Potential for interaction	recommended safety concerns.	
In regards to the pharmacovigilance plan, it is recommended that the sponsor address the following issues: The sponsor states in Part II - Module SII of the RMP; "*No reproductive or developmental toxicity studies were performed with Fluzone Quadrivalent vaccine to date but a Development And Reproductive Toxicity (DART) study with Fluzone Quadrivalent is planned to start in May 2013. The objective of this DART study is to evaluate the effects of the Fluzone Quadrivalent Influenza vaccine on pre- and post-natal development (including an evaluation of teratogenicity) of the rabbit, when a human dose (0.5 mL) is administered by the IM route to females rabbits 24 and 10 days before insemination and on days 6, 12 and 27 of gestation (5 injections).* It is requested that the sponsor discuss how this study results would relate to pregnant human health.	The sponsor has provided a justification in their response.	This is acceptable.
Clinical data is available for children from 6 months to less than 9 years of age and adults of 18 years and older. FluQuadri® /FluQuadri® Junior-are indicated for persons 6 months of age and older. There is CBER (the Centre for Biologics Evaluation and Research) guidance that	The sponsor has provided justification in their response for not proposing additional pharmacovigilance activities for children greater than 9 years. Routine pharmacovigilance is	The justification for not providing clinical data for children aged 9 to 17 years is for final consideration by the Delegate. From a RMP perspective, the

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
the safety and immunogenicity of QIV to children 9 to 17 years of age could be inferred from the safety profiles of QIV in children 6 months to < 9 years of age and in adults 18 years of age and older. Notwithstanding this justification, it is recommended that the sponsor proposes pharmacovigilance activities for adolescents (> 9 years of age).	proposed.	proposed routine pharmacovigilance is acceptable. ACSOV advised that 'data in children/adolescents aged 9 to 17 years' should be included in the RMP as important missing information. This recommendation is endorsed by the evaluator.
Important potential risks in the RMP include "Adverse Events of Special Interest" (AESI) which reflect post market experience for the Fluzone (inactivated TIV), which is not currently registered in Australia. The sponsor states in the RMP; *"Based on the available information from clinical studies GRC43, QIV03 and QIV04 and supportive data from the Applicant's trivalent formulation of Fluzone vaccine, no further risk minimization activities are deemed necessary at this point. No additional pharmacovigilance activities to assess effectiveness of risk minimization measures are ongoing or planned".* In general terms the rationale for the studies is appropriate. However, the sponsor has not provided information for any Australian specific activities. It is noted that Fluzone is currently not registered in Australia. Adverse event rates observed in the clinical trials of a vaccine also cannot be directly compared to rates in the clinical trial of another	The sponsor has advised in their response that they are not planning to conduct any other observational studies beyond a pregnancy registry study in Australia. The sponsor contends that the safety profile is well characterised (according mainly to data for the trivalent formulation) and thus no additional activities are required.	The sponsor's justification is accepted from a RMP standpoint. However the acceptability of a postmarketing safety profile of the quadrivalent vaccine largely extrapolated from the trivalent vaccine is ultimately the decision of the Delegate. ACSOV advised that there should be consideration for class-wide enhanced surveillance of quadrivalent influenza vaccines particularly for the potential risk of febrile seizures.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
vaccine, and may not reflect the rates observed in practice because clinical trials are conducted under different conditions. Hence, it is important that any observational safety study is clearly designed and feasible for implementation in the Australian context. It is currently unclear how or if the sponsor plans on undertaking the studies in Australia.		
It is recommended that the sponsor submits the details on the pregnancy exposure registry to TGA.	*The Pregnancy Exposure Registry Protocol, Pregnancy Data Collection Form and Infant Data Collection Form were included as part of the submission in Annex 3 of Australian Specific Annex (ASA). An updated protocol has been issued in February 2014 and is included with the revised ASA.*	This is acceptable.
To this end it is suggested that the sponsor should provide an attachment to the ASA setting out all the forthcoming studies and the anticipated dates for their submission in Australia.	Details of the only ongoing study (the Pregnancy Exposure Registry) have been included as part of the revised ASA.	This is acceptable.
Any changes to safety information and updated study results must be reported to Australia to ensure these risk minimisation activities remain appropriate for each safety concern.	*Sanofi Pasteur commits to provide timely updates to Australia of any changes to safety information for FluQuadri vaccine. Routine PBRER reports will be provided as per the condition of registration. The PBRER includes pharmacovigilance data from all countries where Fluzone is distributed*	This is acceptable.
In regard to the proposed	*See below*	See below

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
routine risk minimisation activities, it is recommended to the Delegate that the draft PI document be revised as follows:		
The Delegate may wish to replace "Immunisation Handbook" with "Australian Immunisation Handbook" in the proposed Dose and administration Section	*As previously outlined in the response to Recommendation 4 above it is proposed to keep the wording more general in nature based on the intent that this labelling will be applicable in both Australia as well as New Zealand.*	This recommendation is referred to the Delegate for final consideration. ACSOV supported the RMP evaluator's recommendation.
The Delegate may wish to add "Immunisation should not be performed during a febrile or acute illness" under contraindication in the Australian PI in the light of an already approved Australian PI of another influenza vaccine.	*The sponsor agrees and has added an appropriate statement within "Contraindications" section.*	The proposed PI change is noted and referred to the Delegate for final consideration.
The Delegate may wish to add a statement in the draft PI regarding "general advice on overdose management.	*The sponsor agrees and has added language consistent with that included in the PIs for other licensed influenza vaccines.*	The proposed PI change is noted and referred to the Delegate for final consideration.
The Delegate may wish to strengthen the wording in the Australian PI regarding the use of this vaccine in children below the age of 6 months (that is, FluQuadri/FluQuadri Junior are not recommended in children below the age of 6 months).	*The sponsor believes the age indication for FluQuadri is clearly stated in the proposed PI. Therefore, no changes are proposed to be made to this wording.*	The recommendation is referred to the Delegate for final consideration.
The Delegate may wish to add the following statement to the proposed PI for FluQuadri/ FluQuadri Junior about the potential risk of interaction with other medicines: *"Influenza vaccine can impair*	*The sponsor acknowledges the request to add the above advice, which would be consistent with the current Vaxigrip Australian PI; however,*	The proposed PI change is noted and referred to the Delegate for final consideration.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
the metabolism of warfarin, theophylline, phenytoin, phenobarbitone and carbamazepine by the hepatic P450 system. Results from studies have been variable in degree of interaction and time after vaccination for the interaction to take effect. The interaction may be idiosyncratic. Patients taking warfarin, theophylline, phenytoin, phenobarbitone or carbamazepine should be advised of the possibility of an interaction and told to look out for signs of elevated levels of medication. *The immunological response may be diminished if the patient is undergoing immunosuppressant treatment".*	*alternative language is proposed that is consistent with the company's updated core labelling document (CCDS), which will soon be reflected in a new version of the Vaxigrip Australian PI. The proposed language is as follows:* *"Although inhibition of hepatic clearance of phenytoin, theophylline and warfarin has been reported after influenza vaccination, subsequent studies have not shown any evidence of undesirable effects related to this phenomenon."*	
The Delegate may wish to add the following statement in the proposed Australian PI under the Section of "Effects on Laboratory Tests"; *"Following influenza vaccination, false positive results in serology tests using the Enzyme-linked Immunosorbent Assay (ELISA) method to detect antibodies against HIV1, hepatitis C virus and especially Human T-lymphotropic virus Type I (HTLV1) have been observed. The Western Blot technique disproves the results. The transient false positive reactions could be due to the IgM response due to the vaccine".*	*The sponsor agrees and has added proposed wording to the "Effects on Laboratory Tests" section.*	The proposed PI change is noted and referred to the Delegate for final consideration.
In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft CMI	*See below*	See below

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
document be revised as follows:		
That the draft CMI is based on the other approved influenza vaccine marketed by the same sponsor.	*The FluQuadri/FluQuadri Junior CMI have been updated to align with the sponsor's other approved influenza vaccines.*	The proposed changes to the CMI are noted and referred to the Delegate for final consideration.
That advice on an overdose incident is added to the draft CMI.	*Because FluQuadri/FluQuadri Junior is not self-administered, recognition and management of an overdose remains under the purview of the healthcare provider. Accordingly, Sanofi Pasteur believes that information on overdose does not need to be added to a patient-focused labelling document and that the issue of overdose is appropriately addressed in the PI.* *Moreover, administration of 0.5 mL dose to a child younger than 3 years age is not considered to be a safety concern as evidenced by clinical studies demonstrating that a 0.5 mL dose was safe in children 6 months to 35 months of age (inclusive). In addition, at least one national advisory body (National Advisory Committee on Immunization, Public Health Agency of Canada) recommends the 0.5 mL dose in this age group.*	This is acceptable from a RMP standpoint.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
That mention of the potential for interaction is added to the draft CMI.	*To align with the response provided for Recommendation 5 in relation to the PI, it is proposed that no changes are made to the draft CMI for the potential of interactions. The currently proposed statement within the draft PI reads as follows:* *"Although an inhibition of hepatic clearance of phenytoin, theophylline and warfarin has been reported after influenza vaccination, subsequent studies have not shown any evidence of undesirable effects related to this phenomenon."* *A revised CMI taking into consideration updates recommended by the Clinical Evaluator (Question 9) is provided in Annex 2 of the ASA.*	The recommendation is referred to the Delegate for final consideration.

Summary of recommendations

It is considered that the sponsor's response to the TGA request for further information has adequately addressed the issues identified in the RMP evaluation report with the exception of outstanding issues outlined below.

Outstanding issues

Issues in relation to the RMP

The sponsor has proposed a number of Product Information (PI) changes based on the RMP evaluation report. These amendments are for the final consideration of the Delegate.

It is recommended that 'data in children/adolescents aged 9 to 17 years' is included as missing information in the RMP or ASA. This recommendation was supported by Advisory Committee on the Safety of Vaccines (ACSOV).

- Advice from the **Advisory Committee on the Safety of Vaccines (ACSOV)**

The RMP evaluator sought advice from ACSOV regarding the RMP.

Comments on the safety specification of the RMP

Key changes to the updated RMP

In their response to the TGA requests the sponsor provided an updated Australian-specific Annex (version 1.1 dated April 2014). Key changes from the previous version are summarised below (Table 8).

Table 8. Key changes to the RMP

Safety specification	N/A
Pharmacovigilance activities	More information is included regarding the completed studies and ongoing study (pregnancy registry) as part of the pharmacovigilance plan.
Risk minimisation activities	Information has been updated according to recommendations from the RMP evaluation report (see section 5 of this advice).

The evaluator has no objection to the above changes and recommends to the Delegate that the updated version is implemented (see below).

Suggested wording for conditions of registration

RMP

Implement the Core RMP (version 1.0 data lock point 15 March 2013) with Australian Specific Annex (version 1.1 dated April 2014) and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

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

Quality

The quality evaluators recommend that for FluQuadri and FluQuadri Junior 60 µg HA/0.5 mL dose and 30 µg HA/0.25 mL dose, prefilled syringe without needle, with a shelf life of 12 months at 2 to 8^{0}C should be approved. The sponsor has agreed to provide target formulation values to the TGA prior to the commencement of each season.

Nonclinical

The sponsor provided adequate justification for the lack of nonclinical studies for FluQuadri®. There are no nonclinical objections to registration of FluQuadri® and FluQuadri Junior®.

Clinical

Clinical immunogenicity

The three submitted studies are presented involving the different age groups, adults ≥ 18 years, adults ≥ 65 years and children 6 months to <9 years. In each of the studies,

assessment of immunogenicity was the primary objective. No efficacy data was presented. Serum antibody responses to the influenza viruses were considered to correlate with protection against infection and serve as valid surrogates of vaccine efficacy. The method used to measure serum antibodies in the clinical studies was the haemagglutination inhibition (HAI) test.

Assessment of immunogenicity post vaccination was uniform amongst the studies:

- Seroprotection was defined as an HAI antibody titre ≥ 40 (l/dil) at pre and postvaccination
- Seroconversion was defined as a pre-vaccination titre < 10 (1/dil) and a post-vaccination titre ≥ 40 (1/dil), or a pre-vaccination titre ≥ 10 (1/dil) and a ≥ 4 fold increase in postvaccination titre
- Geometric mean titre ratio (GMTR) was calculated postvaccination (GMT QIV/ GMT TIV).

Study GRC43

This study enrolled adults ≥ 18 years. This was a Phase II, open-label, randomised, three-arm, multi-centre study conducted in US in 2009. Vaccine antigen content is described in the clinical evaluation report (CER) Attachment 2. The primary objective was to describe the immunogenicity of the prototype Quadrivalent Influenza Vaccine (QIV) compared with the 2009 to 2010 TIV (B/Brisbane) and the 2008 to 2009 TIV (B/Florida) among adults. The primary endpoint was postvaccination antibody titres for B/Brisbane and B/Florida influenza strains at 21-28 days after vaccination using HAI. Non-inferiority in terms of postvaccination GMT ratios (QIV/TIV) was demonstrated if the lower limit of the two-sided 95% CI was > 2/3 for each of the B virus strains separately. Version 2.0 Clinical Study Report presented results using GRC43 sera retested using optimised turkey red blood cells and 37°C incubation temperature conditions.

A total of 570 adults participated and completed in the study. The full analysis set included In each treatment group 98.4% or higher were included in the full analysis set and the per protocol analysis set. The mean age was around 55 years, with the majority of participants female and Caucasian in all groups.

For the primary objective;

- For strain B/Brisbane, the post-vaccination GMT for QIV (101) was non-inferior to the GMT for the 2009-2010 TIV (114); GMR = 0.89 (95% CI: 0.70 – 1.12)
- For strain B/Florida, the post-vaccination GMT for QIV (155) was non-inferior to the GMT for the 2008-2009 TIV (135); GMR = 1.15 (95% CI: 0.93 – 1.42).

Observational immunogenicity results and immunogenicity results in subgroups are presented in the CER Attachment 2. The QIV vaccine met all three CPMP criteria for all four vaccine strains.

Although not a study objective, results for A/Brisbane and A/Uruguay, for the QIV group compared to the pooled TIV groups were presented in the submission. Non-inferiority in terms described for B strain viruses was shown: GMR = 0.90 (95% CI: 0.70 – 1.15).

The retesting by the optimized HAI assay gave results not materially different to those described in the GRC43 clinical study report previously submitted to CBER.

Study QIV03

This study enrolled adults aged ≥ 65 years. This was a Phase III, randomised, four-arm, active-controlled, multi-centre trial conducted in US in 2010. Treatment groups (investigational QIV; investigation TIV, 2010-2011 TIV; 2010-2011-TIV in 18 to 64 year age range) and vaccine antigen content are described at CER Attachment 2. The primary

objective was to demonstrate non-inferiority of antibody responses to QIV compared with licensed 2010-2011 TIV and investigational TIV assessed by GMTRs for each virus strain at 21 to 28 days postvaccination. Non-inferiority in terms of postvaccination GMT ratios (QIV/TIV) was be demonstrated if the lower limit of the two-sided 95% CI was > 0.66 for each of the four virus strains separately.

A total of 675 participants received one dose of study vaccine and were included in the Safety Analysis Set. The PP Analysis Set included 220 (97.8%) participants in the QIV group, 219 (97.3%) in the 2010-2011 TIV group, and 221 (98.2%) in the investigational TIV group. The mean ages were as 72.4 to 72.8 years. Just over half of each group was female and the majority of participants were Caucasian.

For the primary objective, non-inferiority of GMT ratios was demonstrated for each strain in QIV).

For A/California, the postvaccination GMTR QIV (231)/ pooled TIV (270); GMTR = 0.85 (95% CI: 0.67 – 1.09). For A/Victoria, post-vaccination GMTR QIV (501)/ pooled TIV (324) = 1.55 (95% CI: 1.25 – 1.92). For B/Brisbane, the postvaccination GMTR QIV (73.8)/2010-2011 TIV (57.9) = 1.27 (95% CI: 1.05 – 1.55). For B/Florida, the postvaccination GMTR QIV (61.1)/investigational TIV (54.8) = 1.11 (95% CI: 0.90 – 1.37).

The seroconversion rates after QIV were non-inferior to the control TIVs with respect to all strains except A/H1N1. The criterion for the seroconversion rate to A/H1N1 was marginal. In addition, when comparing antibody responses to each B strain in QIV with those induced by the TIV, that did not contain the corresponding B strain, the seroconversion rates after QIV were superior for each B strain in QIV. The addition of an alternate-lineage B strain into the vaccine formulation did not adversely affect the immunogenicity profile of QIV compared to the currently licensed TIV vaccine. The CER comments that in applying CPMP criteria, each vaccine met each criterion in response to A/California and A/Victoria. Antibody responses to B/strains were less vigorous than to A/strains. Results for B/Florida according to CPMP criteria the QIV and TIV just passed all criteria whereas the B/Brisbane TIV passed none of the criteria.

Study QIV04

This study enrolled children in 2 age strata, 6 months to < 36 months and 3 years to < 9 years. This was a Phase III, randomised, observer-blind, active-controlled, 3-arm multicenter trial conducted in US between 2010 and 2012. The three treatment groups were investigational QIV, 2010-2011 TIV and investigational TIV. Children 6 to <36 months received 0.25 mL doses and children 3 to <9 years received 0.5 mL doses. Previously unvaccinated children received a second dose at Day 28. Vaccine antigen content is presented in the CER Attachment 2.

The primary objective was to assess non-inferiority of QIV antibody responses compared with 2010-2011 TIV and investigational TIV assessed by GMT ratios and seroconversion rates after the final vaccination within each age group (6 to < 36 months and 3 to < 9 years of age) and overall, at 28 to 35 days after final vaccination. Non-inferiority of GMT ratios was demonstrated if the lower limit of the two-sided 95% CI of the GMTR (QIV/TIV) post vaccination was > 0.66 for each of the four virus strains separately within each age group and overall. Non-inferiority of seroconversion rates was demonstrated if the lower limit of the two-sided 95% CI for the difference in seroconversion (QIV–TIV) was > - 10% for each of the four virus strains within each age group and overall.

A total of 4363 participants were randomised, 1851 in the 6 months to <36 month strata and 2511 in the 3 years to < 9 years strata. In total 9.1% of participants were included in full analysis set but excluded from per protocol analysis set. In total 75% received 2 doses of vaccine. In total, mean age was 49.8 months, similar proportions were males and

females and the majority were Caucasians. Demographic and baseline characteristics did not differ substantially between treatment groups overall all or in age strata.

For the primary objective, non-inferiority was shown for all strains for each age strata and overall.

The secondary objective was to demonstrate superiority of GMT ratios and seroconversion rates to each B strain in QIV compared with responses to the TIV not containing the corresponding B strain. Overall and for each age group, superiority was demonstrated for GMT ratios. Seroconversion rates for B strains are presented in the CER Attachment 2.

The study demonstrated that the QIV formulation of influenza vaccine induced antibody responses that were non-inferior to those of the licensed 2010 to 2011 TIV and the investigational TIV with respect to all 4 strains contained in the vaccine overall and among each of the 2 age groups. When comparing antibody responses to each B strain in QIV with those induced by the TIV that did not contain the corresponding B strain the GMT ratios and SC rates after QIV were superior for each B strain in QIV. Post-vaccination HAI antibody responses to strain A/H1N1 and strain A/H3N2 were comparable among the vaccine groups. Post-vaccination antibody responses to the B1 and B2 strains were similar between QIV and 2010 to 2011 TIV groups, and between QIV and investigational TIV groups, respectively.

Safety

Assessment of safety was an observational objective in each of the 3 clinical studies; Study GRC43 in adults ≥18 years and Study QIV03 in adults ≥ 65 years. Solicited local reactions were collected from Day 0 to 3 and solicited systemic reactions from Day 0 to 7 and recorded in a diary card. Safety data were collected at visits at Day 2 and Day 21 to 28.

Adverse events of special interest (Guillain-Barré syndrome, Bell's palsy, encephalitis/myelitis, optic neuritis, Stevens-Johnson syndrome, toxic epidermal necrolysis) were recorded in QIV03 but not GRC43.

There were no reports of unsolicited adverse events in the 20 minutes after vaccination. There were no deaths reported, no serious adverse events considered related to vaccination and no adverse event (AE) of special interest in Study QIV03.

In *Study GRC43*, the frequency of solicited injection site reactions was

QIV	91/190 (47.9%)
2009-2010 TIV	101/190 (53.2%)
2008-2009 TIV V	84 /190 (44.2%)

and the frequency of solicited systemic reactions was

QIV	64/190 (33.7%)
2009-2010 TIV	73/190 (38.4%)
2008-2009 TIV	55/190 (28.9%)

In *Study QIV03***,** the frequency of solicited injection site reactions was

QIV	75/224 (33.5%)
2010-2011 TIV	66/224 (29.5%)
Investigational TIV	54/225 (24.0%)

and the frequency of solicited systemic reactions was

QIV	55/224 (24.6%)
2010-2011 TIV	54/224 (24.1%)
Investigational TIV	47/225 (20.9%)

Study QIV04

This study included a safety analysis set of 1841 children 6 months to 35 months and a total of 2506 children 3 years to < 9 years of age.

The CER agreed with sponsor's conclusions that in the adults studies, the safety profile for QIV was similar to the currently licensed 2010 to 2011 TIV vaccine Fluzone and the investigational TIV. No safety concerns were identified.

In the paediatric study, solicited injection site and systemic reactions, unsolicited AEs, and SAEs were reported at similar rates between the QIV group and the 2 control TIV groups. The safety data from study QIV04 did not raise any safety concerns for QIV. It was reassuring that rates of fever and febrile seizures were not higher among children administered QIV compared with those among children administered the control TIV.

Clinical evaluator's risk benefit assessment

The CER provides a concise summary of immunogenicity and safety results from the 3 submitted studies. The CER concludes that the immunogenicity and safety results of the three studies support the application. Non-inferiority in terms of GMT was shown for both B strains. In GRC43 the QIV met each of the 3 CPMP criteria for each age group. In QIV03, the primary objective was met. Non-inferiority in terms of GMT was shown for all four strains. Observational objectives, non-inferiority in terms of seroconversion and superiority in terms of GMT and seroconversion were met with the exception of marginal non-inferiority of QIV GMTR for A /California. In QIV04, the primary objectives were met. Non-inferiority of QIV GMTs and seroconversion rates was shown for each strain for each age group and overall. The secondary objectives were met. Superiority of QIV was shown for each B strain overall and for both age groups for post-vaccination GMTs and seroconversion rates. The antibody response to B/strains appeared considerably less than that for A/strains and response to each was less for children < 3 years of age and for adults ≥ 65 years of age, that is, those at greatest risk of influenza morbidity and mortality.

Efficacy is inferred; however, future study of efficacy is recommended in the CER. The reported adverse reactions were predominantly of low grade severity and short duration. The safety profile of QIV reported in the three submitted studies was similar to that of the trivalent comparators. No new safety signal was reported.

Clinical evaluator's recommendation

The clinical evaluator recommended registration of FluQuadri for the indication proposed.

An efficacy study was recommended with particular attention to efficacy in children less than 3 years of age and adults ≥ 65 years of age.

Risk management plan

The sponsor's response to the TGA request for further information was considered to adequately address the issues identified in the RMP evaluation report. A number of PI changes which are identified for final consideration of the Delegate and inclusion of ' data in children/adolescents aged 9 to 17 years' should be included as missing information in the RMP or ASA. Advice was sought from the ACSOV regarding the RMP.

Risk-benefit analysis

Delegate's considerations

TIV Fluzone is not a registered vaccine in Australia but has been accepted as an appropriate comparator in the CER based on the longstanding registration status in US and other comparable countries. Clinical studies have also been published comparing immunogenicity and safety of Fluzone with inactivated TIV registered in Australia.

The first round CER raised questions concerning batch consistency and the choice of non-inferiority and superiority margins for immunological criteria in clinical studies which were considered to be adequately addressed by the sponsor in response.

The CER concluded the antibody response to B/strains appeared considerably less than that for A/strains and response to each was less for children < 3 years of age and for adults ≥ 65 years, that is, those at greatest risk of influenza morbidity and mortality. Although the CER recommended registration of FluQuadri for the indications proposed the CER also recommended an efficacy study with particular attention to efficacy in children less than 3 years of age and adults ≥ 65 years.

CHMP/VWP/457259/2014 Guideline on influenza vaccines Non-clinical and clinical module, Draft (open for public consultation until January 2015) includes statements:

> *Due to the lack of evidence to support the ability of inactivated influenza vaccines to elicit protective immune responses and an immune memory response in the youngest groups, the following recommendations are made at the current time. (a) For an indication that includes use in children aged from 6 to 36 months, a demonstration of vaccine efficacy, that is, prevention of influenza in a randomised clinical trial, is required.*
>
> EMA/CHMP/VWP/457259/2014 accepts demonstration of non-inferior immunogenicity as a basis for marketing authorisation application (MAA) in adults including the elderly.

The QIV, Fluarix Tetra, currently registered in Australia has indications for active immunisation of adults and children from 3 years of age.

The Delegate considers Study QIV03 provides adequate support for registration of FluQuadri for adults ≥ 65 years, without a recommendation for conduct of an efficacy study with attention to this age subgroup.

The Delegate considers that Study QIV04 demonstrates non-inferiority of QIV GMTs and seroconversion rates was shown for each strain for each age group and overall compared to an acceptable comparator TIV. This study involved a safety analysis set of 1841 children aged 6 months to 35 months and a total of 2506 children 3 years to < 9 years of age. The safety data from Study QIV04 did not raise any safety concerns for QIV. A number of inactivated influenza vaccines (split virion or subunit) are registered for use in Australia from 6 months of age. On balance, the Delegate considers FluQuadri Junior can be registered for the proposed indications in children aged 6 months to 35 months inclusive. The Delegate recommends a clinical study of protective efficacy with particular attention to this age subgroup study.

Summary of issues

The CER concludes that the immunogenicity and safety results of the three studies, in adults ≥ 18 years, adults ≥ 65 years and children from 6 months to < 9 years of age, support the application. Immunogenicity non-inferiority criteria were met in each of the studies compared to TIV. The safety profiles of QIV and TIV were similar, including rates of fever and febrile convulsions in children. No new safety signal was reported.

No protective efficacy studies were submitted. The CER recommends the immunogenicity and safety data are adequate to support registration for the proposed indication but the CER also recommends conduct of an efficacy study with particular attention to efficacy in children less than 3 years of age and in adults ≥ 65 years.

Draft EMA guidance on influenza vaccines Nonclinical and clinical module (EMA/CHMP/VWP/457259/2014) (open for public consultation) states:

> *Due to the lack of evidence to support the ability of inactivated influenza vaccines to elicit protective immune responses and an immune memory response in the youngest groups, the following recommendations are made at the current time. (a) For an indication that includes use in children aged from 6 to 36 months, a demonstration of vaccine efficacy, i.e. prevention of influenza in a randomised clinical trial, is required. EMA/CHMP/VWP/457259/2014 accepts demonstration of non-inferior immunogenicity as a basis for MAA in adults including the elderly.*

On balance, the Delegate considers Study QIV03 provides adequate support for registration of FluQuadri for adults ≥ 65 years without a recommendation for conduct of a clinical study of protective efficacy in this age subgroup**.**

On balance, the Delegate considers Study QIV04 provides adequate support for FluQuadri Junior to be registered for the proposed indications in children aged 6 months to 35 months inclusive. A clinical study of protective efficacy with particular attention to this age subgroup study is still recommended.

Delegate's proposed action

The Delegate have no reason to say, at this time, that the application for FluQuadri should not be approved for registration The application for FluQuadri Junior is dependent on the ACPM advice that has been sought on the appropriate age subgroups to be included in Indications.

Request for ACPM advice

Advice is sought on whether submitted studies adequately support registration across the age subgroups proposed in Indications.

The committee is requested to provide advice on the following specific issues:

1. Does the submission provide adequate support for use in children aged 6 months to 35 months, given the absence of a clinical study of protective efficacy in this age subgroup?
2. Should a recommendation for conduct of a clinical study of protective efficacy with particular attention to this age subgroup be maintained and made a condition of registration?
3. Does the submission provide adequate support for use in adults aged ≥ 65 years without a recommendation for conduct of a clinical study of protective efficacy with particular attention to this age subgroup?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

The dponsor comments on the issues for which the advice of the ACPM is sought, as outlined in the Delegate's Overview (DO) of 2 September 14, are presented below.

FluQuadri/FluQuadri Junior is an inactivated quadrivalent influenza vaccine (split virion) containing haemagglutinin antigens from two influenza A subtype viruses (H1N1 and H3N2) and two influenza type B viruses (a Yamagata-lineage strain and a Victoria-lineage strain). FluQuadri Junior is the paediatric presentation for children aged 6 months to 35 months who require a 0.25 mL dose.

Since 1987, two distinct lineages of influenza B have circulated worldwide, neither providing good cross-protection against the other. The ability to predict the dominant B lineage during an influenza season has been limited. The rationale for the quadrivalent influenza vaccine (QIV) containing haemagglutinin from both circulating B lineages is to mitigate mismatches between the B lineage chosen for inclusion in the vaccine and the predominant lineage in circulation in a season.

Enhancing protection against influenza B is important for public health across the age spectrum.

The anticipated benefits of FluQuadri/FluQuadri Junior are protection against both B lineages simultaneously without compromising vaccine safety, leading to a reduction in the number of influenza cases, hospitalisations, and deaths by reducing the risk of breakthrough influenza infection due to mismatch.

The burden of influenza, including Influenza B is high in infants and young children, who are more likely to require hospitalisation due to complications following influenza infection. Influenza B infection is also prominent in the elderly, leading to excess mortality in some annual epidemics.

The development of quadrivalent FluQuadri/FluQuadri Junior builds on the experience of trivalent Fluzone vaccine, which is manufactured and registered in the US. The only material difference between trivalent Fluzone (TIV) vaccine and quadrivalent FluQuadri (QIV) vaccine is the addition of a second B strain from the alternate lineage. Both Fluzone and Fluzone Quadrivalent (the trade name for FluQuadri/FluQuadri Junior in the US) are approved by the FDA for use in ages 6 months and older.

The effectiveness of Fluzone has been demonstrated over more than 20 years with worldwide experience of over a billion doses confirming a very good safety profile across the spectrum of population sub-groups from infants to elderly.

Following the 2013 to 14 Northern Hemisphere influenza season, newly available cumulative postmarketing exposure for Fluzone Quadrivalent as of 15 February 2014 is over 7 million vaccinees with no new safety signals identified. In clinical studies, FluQuadri/FluQuadri Junior (QIV) has shown non-inferior immunogenicity and comparable safety to Fluzone (TIV).

As noted by the Delegate, Fluzone is considered an appropriate comparator based on its long-standing registration status in the US and other countries, including Canada, and considering it only materially differs from FluQuadri/FluQuadri Junior with regards to the inclusion of an additional B strain from the alternate lineage.

The available clinical data meets the requirements for demonstration of safety and effectiveness based on immunogenicity as a surrogate for efficacy, as outlined in the current EU guidance CPMP/BWP/214/96.[2]

Based on the evidence from clinical studies and extensive post marketing experience for both the trivalent and quadrivalent vaccines in the US (Fluzone/Fluzone Quadrivalent), the sponsor considers that the application for FluQuadri/FluQuadri Junior has been adequately supported to justify approval in all population sub-groups, in alignment with the existing registration in the US.

The sponsor comments on the specific issues for which advice is sought from the ACPM are outlined below.

1. *Does the submission provide adequate support for use in children aged 6 months to 35 months, given the absence of a clinical study of protective efficacy in this age subgroup?*
2. *Should a recommendation for conduct of a clinical study of protective efficacy with particular attention to this age subgroup be maintained and made a condition of registration?*

FluQuadri/FluQuadri junior has been approved under different trade name in the US as well as a number of other countries including Canada (see Regulatory Status). No other agency has requested the conduct of an efficacy study to support registration based on the extensive history of use of the antigenic components in TIV vaccines.

Sanofi Pasteur worked closely with the US Food and Drug Administration's Center for Biologics Evaluation and Research (CBER) during the planning and execution of the FluQuadri clinical development program. CBER did not require that an efficacy study of FluQuadri be conducted.

Instead the agency considered efficacy data for trivalent Fluzone vaccine as supportive. CBER approved Fluzone Quadrivalent (the trade name for FluQuadri/FluQuadri Junior in the US) based on:

- Non-inferiority criteria for immunogenicity used in the clinical studies are well recognised and appropriate
- Results of the studies demonstrated the non-inferiority (and superiority) to TIV in all age groups
- These immunogenicity results indicate that Fluzone Quadrivalent is very likely to confer protection against influenza similar to that provided by Fluzone for the strains common to both vaccines, and additional protection for the alternate B lineage over that provided by the TIV
- The safety database for Fluzone Quadrivalent clinical studies is of adequate size to support approval
- The risks of vaccination with Fluzone Quadrivalent appear to be minor, and similar to that associated with Fluzone.

Furthermore, conduct of a placebo-controlled efficacy trial in the US was not possible because during the clinical development of Fluzone Quadrivalent vaccine, influenza vaccine was (and still is) recommended for all children 6 months of age and older. Therefore, it would be unethical to randomise children to a placebo control. Further, it would be impossible to design a relative efficacy trial of FluQuadri versus trivalent Fluzone vaccine because one could never know if the B lineage not contained in the trivalent vaccine would circulate widely in any given upcoming season. These same challenges would apply to conduct of a clinical study in Australia.

The sponsor acknowledges that the draft EU guidance CHMP/VMP/457259/2014 which is currently open for consultation, as referenced by the Delegate, includes requirements for demonstration of vaccine efficacy for children aged 6 to 36 months. The clinical program for FluQuadri/FluQudari Junior has had been completed prior to this draft guidance being released.

Considering the extensive postmarketing experience for the antigenic components in FluQuadri/FluQuadri Junior and the similarity of populations and demographics between the US and Australia, the sponsor does not consider that retrospective application of EU guidance, particularly when only in draft, is warranted based on the evidence as outlined below:

- The only material difference between trivalent Fluzone vaccine and FluQuadri is the addition of a B strain from the alternate lineage. Accordingly, the experience of trivalent Fluzone vaccine is relevant
- Efficacy of trivalent Fluzone vaccine in preventing laboratory-confirmed influenza illness was assessed as a secondary objective in a randomised, double-blind, placebo-controlled study that was conducted over 2 seasons during 1999 to 2001 in 2 separate cohorts of children 6 through 24 months of age. Two 0.25 mL doses of trivalent Fluzone vaccine or placebo were administered to study subjects
- Seroconversion rates were 88.6% to 96.8%, depending on the strain and season
- Vaccine efficacy during the 1999 to 2000 season was 66% (95% CI, 34% to 82%). During the second year of the study (2000 to 2001), there was scant circulation of influenza, so efficacy could not be assessed adequately. The culture-confirmed influenza attack rates during the two seasons were 15.9% and 3.3% in the placebo groups respectively
- This study demonstrated that trivalent Fluzone vaccine is effective at preventing influenza illness in 6 to 24 month old children when influenza circulation can be detected in the community[5]
- The demonstration of efficacy of trivalent Fluzone vaccine in Year 1 of the above study, together with the demonstration of immune responses following FluQuadri Junior vaccine that were non-inferior to those following use of trivalent Fluzone vaccine in the subset of children 6 months through 35 months of age in QIV04, is supportive of the protective efficacy of FluQuadri Junior in this population
- Lack of efficacy is monitored through routine pharmacovigilance activities and reported in annual Periodic Benefit-Risk Evaluation Reports (PBRER). Since its launch in the 2013 to 2014 Northern Hemisphere influenza season in the US, no cases of lack of efficacy were reported for Fluzone Quadrivalent cumulative to 15 February 2014. In addition, to the non-inferiority demonstration, the immunogenicity data presented in this application are also compared with the requirements of the European Medicines Agency criteria for demonstration of immunogenicity (Committee for Medicinal Products for Human Use (CHMP) Note for Guidance (NfG) CPMP/BWP/214/96), which is the current European Guideline adopted by the TGA. Although this guidance does not include specific criteria for paediatric vaccines, FluQuadri met the adult CHMP criteria in QIV04 subjects 6 months to > 9 years of age.

Overall the sponsor considers that the evidence from clinical studies and extensive postmarketing experience for both the trivalent and quadrivalent vaccines in the US (Fluzone/Fluzone Quadrivalent) confirms a favourable benefit-risk profile in all age sub-groups. On this basis, there is no justification or ethical duty for the requirement to conduct a clinical study of protective efficacy in children aged 6 to 35 months.

3. *Does the submission provide adequate support for use in adults aged ≥ 65 years without a recommendation for conduct of a clinical study of protective efficacy with particular attention to this age group?*

[5] Hoberman A, Greenberg DP, Paradise JL, et al. Effectiveness of Inactivated Influenza Vaccine in Preventing Acute Otitis Media in Young Children. JAMA. 2003;290:1608-1616

The sponsor concurs with the Delegate's recommendation that the submitted clinical data adequately supports use in adults aged ≥ 65 years and conduct of an efficacy study in this specific population is not required. Older age groups are recognised as being at increased risk for influenza-related complications and studies have shown that influenza vaccination has been beneficial in preventing such complications. Accordingly, conducting a placebo-controlled trial to assess the efficacy of FluQuadri in this population would also pose ethical challenges.

In clinical studies, serum antibody responses to the influenza viruses were considered to correlate with protection against infection and serve as valid surrogates of vaccine efficacy. As demonstrated in QIV03, immune responses following use of FluQuadri vaccine in adults ≥ 65 years of age were non-inferior to the immune responses following use of the trivalent controls with respect to the influenza strains contained in each. Moreover, immune responses induced by FluQuadri were compliant with the requirements of the current EU guidance CPMP/BWP/214/96[2] which reflect the accepted standards for clinical studies in place at the time the clinical program was conducted. On this basis the sponsor has met the requirements to support use in adults aged ≥ 65 years with further reassurance provided by the accumulated postmarketing experience following the 2013 to 2014 Northern Hemisphere influenza season.

4. *RMP evaluation: 'data in children / adolescents aged 9 to 17 years' should be included as missing information in the RMP or ASA*

As previously outlined, since launch of Fluzone Quadrivalent in the US during the 2013 to 2014 Northern Hemisphere influenza season over 7 million doses were distributed as of 15 February 2014. The most recent PBRER and its Addendum Report provided as part of this response confirms no new safety concerns from postmarketing experience and no findings specific to children aged 9 to 17 years. Further reassurance on safety and immunogenicity is provided by over which supports approval of FluQuadri without restriction of the population age range.

It has also been previously noted that Sanofi Pasteur worked closely with CBER during the planning and execution of the FluQuadri clinical development program and that CBER advised that the safety and immunogenicity of the vaccine in children 9 to 17 years of age could be inferred from the demonstration of the vaccine's safety and immunogenicity in children 6 months to < 9 years of age (Study QIV04) and in adults ≥ 18 years of age and older (Study GRC43). Indeed, findings from GRC43, QIV03 and QIV04 showed that FluQuadri was safe in children, adults and the elderly, and induced immune responses that were comparable to those induced by trivalent Fluzone vaccine with respect to corresponding strains.

On the basis of the postmarketing experience accumulated for both the quadrivalent and trivalent vaccines, the sponsor does not consider that the proposed amendments to the ASA are warranted.

Summary

In summary, FluQuadri/FluQuadri Junior has the potential to mitigate the impact of mismatches between the B-lineage strain chosen for inclusion in the vaccine and the one subsequently that predominately circulates, thereby representing an important tool in the control of influenza, especially for vulnerable populations including infants, young children and the elderly:

- Fluzone Quadrivalent (the trade name for FluQuadri/FluQuadri Junior in the US) is approved in both the US and Canada for use in persons 6 months of age and older
- The evidence from clinical studies and extensive post marketing experience for both the trivalent and quadrivalent vaccines in the US (Fluzone/Fluzone Quadrivalent) confirms a favourable benefit-risk profile in all age sub-groups

- The available clinical data meets the requirements for demonstration of safety and effectiveness based on immunogenicity as a surrogate for efficacy, as outlined in the current EU guidance CPMP/BWP/214/96[2]
- Considering the similarity of populations and demographics between the US and Australia further conduct of an Australian specific protective efficacy study in children aged 6 to 35 months of age is not considered warranted as a condition of registration
- Routine pharmacovigilance post approval will ensure reports of lack of efficacy are monitored and reported in the annual Periodic Benefit-Risk Evaluation Report (PBRER). Based on the extensive postmarketing experience with the vaccine antigens this approach is considered sufficient to assess ongoing benefit/risk in all age sub-groups. The sponsor therefore considers that the application for FluQuadri/FluQuadri Junior has been adequately supported to justify approval in all population sub-groups, based on the favourable benefit/risk profile including the enhanced protection against influenza B, which will assist in addressing an important clinical and public health need in managing the impact of influenza on the Australian population during seasonal epidemics.

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 submission seeks to register a new chemical entity.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered FluQuadri and FluQuadri Junior, suspension for injection containing Influenza Virus Haemagglutinin H1N1 15/ 7.5 µg/mL; Influenza Virus Haemagglutinin H3N2 15/ 7.5 µg/mL; Influenza Virus Haemagglutinin B Victoria lineage 15/ 7.5 µg /mL and Influenza Virus Haemagglutinin B Yamagata lineage 15/ 7.5 µg/mL to have an overall positive benefit–risk profile for the amended indication**;**

> *FluQuadri is indicated for active immunisation against disease caused by influenza A subtype viruses and type B viruses contained in the vaccine.*
>
> *FluQuadri is indicated for use in adults and children 3 years and older.*
>
> *FluQuadri Junior is indicated for use in children aged 6 months to 35 months inclusive.*

In making this recommendation the ACPM noted that while FluQuadri was shown to be less immunogenic in those at greatest risk of influenza morbidity and mortality (children < 3 years of age and adults ≥ 65 years), this is true for all influenza vaccines evaluated thus far.

The ACPM was concerned at the possibly higher incidence of febrile seizures post influenza vaccination in children and considered this should be the subject of post marketing monitoring through the RMP and that the PI and CMI should also contain suitable statements.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

- Negotiation of Product Information and Consumer Medicines Information to the satisfaction of the TGA

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

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised the following;

- The addition in the Dosage and Administration section of the statement
  - *The use of FluQuadri should be guided by official recommendations.*
- Statements in the PI and relevant sections of the CMI on the possibility of febrile seizures in children, following *FluQuadri* vaccination.

Specific advice

The ACPM advised the following in response to the delegate's specific questions on this submission.

1. Does the submission provide adequate support for use in children aged 6 months to 35 months, given the absence of a clinical study of protective efficacy in this age subgroup.

   The ACPM advised that the evidence submitted was sufficient to show that FluQuadri was immunogenic and safe across all age subgroups. While the quadrivalent vaccine was less immunogenic in children than in adults, there appears to be no cost in terms of serological responses or adverse events in adding the fourth (B) strain to a well-established trivalent vaccine. The extensive post marketing data on the well-established trivalent vaccine support safety.

2. Should a recommendation for conduct of a clinical study of protective efficacy with particular attention to this age subgroup be maintained and made a condition of registration?

   The ACPM noted that the requirement of the draft EMA guideline (Influenza vaccine, Non-clinical and clinical module) for demonstrating clinical efficacy in children 6 to 35 months has ***not*** *been met but the ACPM was not of the view that submission of such a trial should precede registration. The ACPM understands that such a clinical study may be required by EMA and if conducted then submission of the analysis report would be appropriate. The draft EMA guidance also a recommendation for conduct of product –specific vaccine effectiveness studies for seasonal influenza vaccines which would also be a potential source of relevant information.*

3. Does the submission provide adequate support for use in adults aged > 65 years without a recommendation for conduct of a clinical study of protective efficacy with particular attention to this age subgroup?

   The evidence submitted was sufficient to show that FluQuadri was immunogenic and safe across all age subgroups. While the quadrivalent vaccine was also less immunogenic in the elderly than in younger adults, there appears to be no cost in terms of serological responses or adverse events in adding the fourth (B) strain to a well-established trivalent vaccine. The extensive post marketing data on the well-established trivalent vaccine support safety.

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 these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of FluQuadri Inactivated Quadrivalent Influenza Vaccine (Split Virion), Influenza virus haemagglutinin 60mcg, 0.5mL suspension for injection in pre-filled syringe; and FluQuadri Junior Inactivated Quadrivalent Influenza Vaccine (Split Virion), Influenza virus haemagglutinin 30mcg, 0.25mL suspension for injection in pre-filled syringe for intramuscular injection, indicated for:

> *FluQuadri and FluQuadri Junior are indicated for active immunisation of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine*
>
> *FluQuadri is indicated for use in adults and children 3 years and older*
>
> *FluQuadri Junior is indicated for use in children aged 6 months to 35 months inclusive.*

Specific conditions of registration applying to these goods

1. Risk management Plan: The FluQuadri and FluQuadri Junior Inactivated Quadrivalent Influenza Vaccine (Split Virion) Risk Management Plan (Core RMP) (version 1.0 data lock point 15 March 2013) with Australian Specific Annex (version 1.2 dated November 2014) and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
2. Batch Release Conditions of Registration: It is a condition of registration that all independent batches of Fluquadri and FluQuadri Junior 60 mcg HA/0.5 mL dose and 30 mcg HA/0.25 mL dose, prefilled syringe without needle 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).

Attachment 1. Product Information

The Product Information approved for main FluQuadri/FluQuadri Junior at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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