Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Inactivated quadrivalent influenza vaccine (split virion)

Proprietary Product Name: Afluria Quad

Sponsor: Seqirus Pty Ltd

July 2017

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 <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (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; it provides 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

Common abbreviations

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
ACSOM	Advisory Committee on the Safety of Medicines
ACSOV	Advisory Committee on the Safety of Vaccines
ADR	Adverse Drug Reaction
AE	Adverse event
AESI	Adverse event of special interest
ACIR	Australian Childhood Immunisation Register
AIVC	Australian Influenza Vaccine Committee
ARTG	Australian Register of Therapeutic Goods
ASA	Australian-specific annex
ASR	Annual Safety Report
ASU	Annual (influenza) strain update
ATAGI	Australian Technical Advisory Group on Immunisation
BPL	Propiolactone
CBER	Center for Biological Evaluation and Research (US)
CDC	Centers for Disease Control and Prevention (US)
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMI	Consumer medicines information
DHCP(L)	Dear Healthcare Professional (Letter)
DSMB	Data and Safety Monitoring Board
DSUR	Developmental Safety Update Report
EMA	European Medicines Agency
FAS	Full analysis set
FBV	Final bulk vaccine

Abbreviation	Meaning
FDA	Food and Drug Administration (US)
FDL	Final dispensed lot
GMFI	Geometric Mean Fold increase
GLM	General linear model
GMT	Geometric mean titres
HA	Haemagglutinin
HAI	Haemagglutinin inhibition
HCP	Healthcare professional
HI	Haemagglutination inhibition
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
ILI	Influenza-like illness
IZP	Inactivated zonal pool
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MPH	Monovalent pooled harvest
NA	Neuraminidase
NIP	National Immunisation Program
NOCI	New onset of chronic illness
ODT	Optical density turbidity
Ph Eur	European Pharmacopoeia
PK	Pharmacokinetic
PI	Product Information
PP	Per-protocol (population)
PSUR	Periodic Safety Update Report
QIV	Quadrivalent Influenza Vaccine

Abbreviation	Meaning
RMP	Risk Management Plan
RT-PCR	Real-time polymerase chain reaction
SAE	Serious adverse event
SCR	Seroconversion rate
SOP	Standard Operating Procedure
SPR	Seroprotection rate
SRD	Single radial immunodiffusion
TDOC	Taurodeoxycholate
TGA	Therapeutic Goods Administration
TIV	Trivalent Influenza Vaccine
VRBPAC	Vaccines and Related Biological Products Advisory Committee (FDA)
w/v	Weight/volume
WHO	World Health Organisation

I. Introduction to product submission

Submission details

Type of submission:	New chemical/biological entity
Decision:	Approved
Date of decision:	15 July 2016
Date of entry onto ARTG	22 July 2016
Active ingredient(s):	Influenza virus haemagglutinin[1]
Product name(s):	Afluria Quad
Sponsor's name and address:	Seqirus Pty Ltd 63 Poplar Road, Parkville, VIC 3052
Dose form(s):	Suspension for injection
Strength(s):	60 µg total influenza virus haemagglutinin/dose[1]
Container(s):	Pre-filled syringe
Pack size(s):	1 x 0.5 mL syringe; and 10 x 0.5 mL syringes
Approved therapeutic use:	*For the prevention of influenza caused by Influenza Virus, Types A and B contained in the vaccine. The vaccine is indicated for use only in persons aged 18 years and over.* *See Precautions and Dosage and Administration.* *For full details regarding recommendations for influenza vaccination, please refer to the relevant national immunisation guidelines.*
Route(s) of administration:	Intramuscular; subcutaneous
Dosage:	A single dose of 0.5 mL in adults ≥ 18 years administered by intramuscular or deep subcutaneous injection. Immunisation should be undertaken in anticipation of seasonal outbreaks of influenza. To provide continuing protection, annual vaccination with vaccine containing the most recent strains is necessary.
ARTG number (s):	262428

[1] The suspension includes four inactivated, split influenza virus strains; two type A strain subtypes and two type B strains from separate lineages as recommended by the Australian Influenza Vaccine Committee for that season. Each 0.5 mL dose contains 15 µg of inactivated influenza virus haemagglutinin from each of the four influenza virus strains, giving a total 60 µg influenza virus haemagglutinin per 0.5 mL dose.

Product background

This AusPAR describes the application by the sponsor to register Afluria Quad, split virion inactivated quadrivalent influenza vaccine (QIV), containing a total of 60 µg of influenza virus haemagglutinin (HA). The sponsor applied for the following indications:

> *'For the prevention of influenza caused by Influenza Virus, Types A and B contained in the vaccine. The vaccine is indicated for use only in persons aged 18 years and over.'*

This is an application by the sponsor to register a viral vaccine (influenza vaccines) for prophylaxis against influenza. HA and neuraminidase antigens present in the vaccine induce a protective antibody response in vaccinated individuals within 2 to 3 weeks after immunisation. The 0.5 mL suspension includes four inactivated, split influenza virus strains; two type A strain subtypes and two type B strains from separate lineages (15 µg HA for each) as recommended by the Australian Influenza Vaccine Committee for that season. It has the Anatomical Therapeutic Chemical (ATC) code of J07BB02.[2]

The chemistry, manufacture, and control of QIV is the same as that described for Seqirus trivalent influenza vaccine (TIV) (licensed in Australia with the tradename Fluvax) except for the inclusion of an alternate lineage influenza B strain which increases the total HA content from 45 to 60 µg per 0.5 mL dose. TIVs contain antigens from the B-strain lineage predicted to be most prevalent. Such vaccines provide limited immunity against B strains of the lineage not included in the vaccine. Development of a QIV, including B strains of both lineages, is expected to improve vaccine protection in target populations. Vaccine strain composition is based on the seasonal recommendations of the World Health Organization (WHO). Following registration of an influenza vaccine product, the Australian Influenza Vaccine Committee (AIVC) reviews and evaluates data relating to the strains of influenza that were circulating in Australia and the Southern Hemisphere in the preceding winter in conjunction with WHO guidelines and may make recommendations about changes to the strains recommended to be covered by the seasonal influenza vaccine.

The name of the sponsor was bioCSL at the time of submission, but has since changed name to Seqirus Pty Ltd during the evaluation of this QIV.

The proposed tradename for the QIV was originally Fluvax Quad but was later changed to Afluria Quad following discussion with the TGA, with specialist input and recommendations from the Australian Technical Advisory Group on Immunisation (ATAGI) as described in this document.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 22 July 2016.

At the time the TGA considered this application, a similar application for a quadrivalent vaccine was submitted to the Food and Drug Administration (FDA) of the United States (US) on 27 October 2015 with an action due date 27 August 2016. The indication sought was:

> *'Active immunization against influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine for persons 18 years of age and older'.*

[2] World Health Organization Collaborating Centre for Drug Statistics Methodology (WHOCC) Anatomical Therapeutic Chemical (ATC) Classification System.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Drug substance (active ingredient)

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

Manufacture

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

This drug substance is manufactured using conventional egg inoculation, harvest, inactivation and purification procedures. The virus is inoculated in embryonated hen's eggs, incubated and purified by zonal centrifugation on a sucrose gradient. The concentrated zonal pool is inactivated with beta-propiolactone before it is split to disrupt virus particles using sodium taurodeoxycholate (TDOC). The inactivated, split virus concentrate is diafiltered and volume adjusted to meet target haemagglutinin (HA) concentration.

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.

During initial evaluation the quality evaluator raised concerns about several areas around the characterisation of MPHs. These are summarised in the quality summary and conclusions at the end of this section. Briefly, it is worth noting that the sponsor has agreed to an update of the current characterisation protocol for new MPH strains to include a range of additional parameters. Most notable amongst these additional parameters are the characterisation of lipid and RNA content. These are notable because of their association with paediatric febrile events linked with the 2010 trivalent Fluvax.[3] It is therefore important that these are well characterised and controlled. This will be particularly important consideration in any future product intended for use in a paediatric population.

The previously approved hold time for the inactivated zonal pool (IZP) was determined from a series of studies that were carried out some considerable time ago. Since that time there have been a number of changes to the manufacturing process that may have had an impact on the IZP and consequently its storage and processing properties. The risk to the quality of the product arising from the issue identified with the IZP hold time is relatively low at the present time but remains undefined due to a lack of quality data. It will be difficult to approve future changes in manufacturing practices without this baseline data to indicate the IZP (including hold time) produces a well characterised and consistent

[3] Rockman et al., Role of viral RNA and lipid in the adverse events associated with the 2010 Southern Hemisphere trivalent influenza vaccine. Volume 32, Issue 30, 2014, Pages 3869–3876.

intermediate. It is important that suitable data be generated to support an IZP hold time for current manufacturing practices.

All sterility and endotoxin issues have been resolved.

All manufacturing issues have not been resolved. Please refer to the quality summary and conclusions at the end of this section.

Specifications

The proposed specifications, which control identity, content, potency, purity and other biological and physical properties of the drug substance relevant to the dose form and its intended clinical use. These specifications are in line with the European Pharmacopoeia (Ph Eur) guidance and/or acceptable for controlling the drug substance.

The current procedure used as part of the characterisation protocol) and as an orthologous check on the Percentage HA Profile test , does not provide the appropriate support for the test and the quantification of virus particles in other preparations such as seed stocks and zonal pools. It is important that a more quantitative methodology is included so that clear estimates of concentration of virus particles can be made. During the initial evaluation, the quality evaluator requested that an updated quantification methodology for virus particles or alternative methodologies be developed to provide suitable testing of the working seed lot and MPHs and to improve characterisation. The sponsor agreed to the request and this issue was resolved.

Stability

All data provided supports the 12 months 2 to 8°C shelf life for MPH of influenza vaccine strains.

Risk of adventitious agents

The sponsor was requested (via a TGA consolidated request) to provide further evidence (that is in compliance with Ph Eur monograph 2.6.16) for how the risk of contamination introduced during manufacture has been controlled to an acceptable level.

These issues were required to be resolved under the condition that was placed on the registration of Afluria Quad. The issues were later resolved. Please refer to the quality summary and conclusions at the end of this section.

Drug product

Manufacture

The manufacturing process, equipment, fill and final container for QIV are based on the registered TIV, Fluvax. The manufacturing process of QIV involves the combination of four influenza virus strains and vaccine diluent in suitable proportions to ensure a minimum concentration of 30 µg/mL of the influenza virus antigen, HA, is present per strain. The product is manufactured by formulating MPHs with the appropriate amount of diluent to generate the final bulk vaccine (FBV). The FBV is aseptically filled into syringes (final dispensed lot (FDL)), then inspected, labelled and packaged as the final drug product. This is subject to batch release.

Specifications

Release test is performed at the stage of FBV, FDL, or MPH. All specifications meet or exceed those defined in the Ph Eur for the final lot. The sponsor commits to provide FBV potency data for initial lots produced to demonstrate that the formulation is in agreement with the calculated range.

The specifications are in line with the Ph Eur guidance and/or acceptable for controlling the drug product. However, there are limited characterisation studies which would provide information about product consistency from season to season to enhance process and product understanding.

Presence of aggregates

The quality evaluator requested the sponsor address the potential of the drug product to aggregate for in the QIV. The sponsor provided a report and characterisation studies and has committed to carry out further studies on the presence and nature of aggregates.

Formulation

Afluria Quad (QIV) is supplied as a single dose, 0.5 mL prefilled syringe, containing a sterile, aqueous, suspension for injection. It includes four approved influenza virus (types A and B) strains, including two A strains (H1N1 and H3N2) and two B strains (Victoria lineage and Yamagata lineage).

The total HA content is 60 µg/dose. The product complies with the minimum standards as defined in the Inactivated Influenza Vaccine (Ph Eur monograph 0158) for HA content per strain per dose. The vaccine diluent used has the same composition as that used to formulate TIV.

The nominal HA concentration is ≥ 15 µg/dose for each strain (30 µg/mL per strain). However, the drug product is formulated to a target strain specific HA concentration to ensure minimum release specification is met at the end of the shelf life. The sponsor provided a method and justification to support calculation of these strain specific targets.

The potency evaluator raised issues with the potency estimation differences between target, release and clinical trial lots.

Stability

The stability study results support a shelf life of up to 12 months at 2 to 8˚C.

Biopharmaceutics

Biopharmaceutic data are not required for this product.

Quality summary and conclusions

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

The quality evaluation of Afluria Quad (QIV) raised the following issues:

1. The proposed range of splitting conditions for the drug substance are not supported by the splitting concentrations used for the single final lot of product used in the clinical trial.

2. The characterisation of the drug substance and the lack of testing for parameters such as lipid and RNA content. It was recommended that an updated characterisation protocol be made available to the TGA prior to the 2017 Annual Strain Update.
3. The risk to the product from adventitious agents.
4. The lack of a quantitative methodology for estimating the virus particle concentration in the drug substance and other materials e.g. working seeds.
5. The colour of the syringe labelling and possible confusion with other products
6. The differences in the potency estimation methods proposed for release lots and those used for the clinical trial lot.
7. The annual SRD qualification procedure and the parameters assessed during that process.
8. The presence and characteristics of aggregates in the drug substance and the drug product.

The sponsor responded to these issues as part of the ACPM process and they were resolved through a series of on-going commitments and undertakings. Please refer to the outcomes section at the end of this document.

Batch release conditions of registration for clinical delegate

Should the product be approved, details of the specific requirements associated with batch release and testing will be forwarded to the Delegate prior to finalisation of administrative and registration activities.

III. Nonclinical findings

The chemistry, manufacture and control of the QIV are the same as for the registered TIV, with the exception that it contains a fourth influenza strain, resulting in a total HA content of 60 µg per 0.5 mL rather than 45 µg per 0.5 mL.

No nonclinical studies were submitted. The lack of studies was justified in the nonclinical overview on the basis of prior marketing experience with the TIV and clinical trial data for the QIV.

The Fluvax TIV is a grandfathered product. One embryofetal development study was conducted with Fluvax TIV. The study showed no effects on rat mating, fertility, and embryofetal or pup development.

The registered QIVs Fluarix Tetra (GlaxoSmithKline) and FluQuadri (Sanofi Pasteur) have been assigned an Australian pregnancy category of B1.[4]

At the pre-submission meeting the sponsor was advised that, although not essential for registration, an embryofetal development study with the QIV would provide additional assurance regarding safe use in pregnancy.

Impurities

The specified and calculated levels of impurities in the QIV raise no toxicological concerns.

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

Nonclinical summary and conclusions

There are no nonclinical objections to registration of the inactivated QIV Afluria Quad.

Amendments to the draft PI were recommended.

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

Afluria Quad clinical rationale

Influenza, a respiratory orthomyxovirus, is a seasonal infectious disease that occurs in epidemics throughout the northern and southern hemisphere winter months, and leads to considerable morbidity and mortality globally in all age groups. In general, influenza is resolved within two to seven days, although symptoms of cough and malaise may be prolonged. However, for some population groups, notably the elderly and those with chronic diseases (for example pulmonary or circulatory disorders, metabolic disorders such as diabetes mellitus, renal dysfunction, or immunosuppression), influenza can exacerbate underlying medical conditions and/or lead to secondary viral or bacterial pneumonia.[5,6] During influenza epidemics, there is an increased mortality risk among older adults (age > 65 years), people with chronic diseases, and very young children (age 0 to 12 months), as well as an increase in morbidity and hospitalization because of influenza-associated complications.[5,7]

Influenza A and B cause most human disease. Influenza A viruses are divided into subtypes based on two viral external proteins, the HA and the neuraminidase (NA).

Of the influenza type A virus subtypes, the A/H3N2 and A/H1N1 subtypes are clinically the most important. Influenza type B viruses show extensive variation in antigenicity. Influenza B viruses are separated into two distinct genetic lineages, Yamagata and Victoria. In terms of infection, influenza type A viruses have been isolated from several non-human species, including birds, horses, and swine, whereas influenza type B viruses almost exclusively affect humans.

The influenza A or B surface glycoprotein HA is the key antigen involved in attachment of the virus to receptors on respiratory epithelial cells, whereas the NA glycoprotein is involved in release of the virus from the cell surface. During infection, the virus stimulates production of antibodies in the serum (immunoglobulin G) and nasal secretions (immunoglobulin A) to these surface glycoproteins. High levels of virus type-specific antibodies are associated with protection from disease due to infections with homologous and closely related influenza virus trains.[5,8] Novel influenza strains arise from antigenic drift due to point mutation and recombination events that occur during viral replication. These events result in the emergence of new strains of the influenza virus capable of causing epidemics, as pre-existing antibodies resulting from previous virus exposure or vaccination are generally not cross-protective.[8] Influenza type A is capable of major

[5] Fiore A, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR Recomm Rep 2009 Jul 31;58(RR-8):1-52.
[6] Rothberg M, et al., Complications of viral influenza. Am J Med 2008 Apr;121(4):258-64
[7] Monto A, Epidemiology of influenza. Vaccine. 2008 Sep 12; 26 Suppl 4:D45-8.
[8] Hay A, et al., Influenza viruses. In: Belshe RB, ed. Textbook of Human Virology. St. Louis, Missouri: Mosby Year Book, Inc, 1991;307–341.

antigenic shifts when a novel HA emerges from re-assortment with an animal influenza virus. Influenza B undergoes less rapid antigenic drift that is, is generally more stable, than influenza A. When a new subtype of influenza virus emerges, all individuals are susceptible to infection except those who have lived through earlier epidemics with a related virus subtype. Infection produces immunity to the specific virus; however, the length and extent of immunity is dependent on the degree of antigenic shift, the number of previous infections, and the immune status of the individual.[9]

Influenza epidemics have been associated with the circulation of type A/H3N2, type A/H1N1, and type B viruses, either individually or together. Two genetically distinct lineages of influenza B viruses have co-circulated since 1985.[10] The burden of infection is largely on school age children, young adults, and the elderly.[11] In the US, B viruses account for 24% of positive specimens and 34% of reported paediatric influenza deaths.[12]

Prevention: Prevention of influenza illness is achieved by annual prophylactic immunisation. The US Centers for Disease Control and Prevention (CDC), in response to the A/H1N1 pandemic in 2009 that disproportionately affected healthy young people, revised their recommendations in 2010, calling for annual immunisation of the entire US population. Previously, only those at increased risk for influenza, including the very young, elderly, chronically ill, and health care workers were advised to be vaccinated annually. In Australia, annual influenza vaccination is currently recommended for any person ≥ 6 months of age who wishes to reduce the likelihood of becoming ill with influenza. Annual influenza vaccination is strongly recommended for individuals at increased risk of influenza complications including those with co-morbidities including being immunocompromised for whatever reason.

Rationale for quadrivalent versus trivalent vaccines: Influenza vaccines have historically been trivalent, including variants of A/H3N2, A/H1N1, and one B-strain lineage. HA and, to some extent, NA antigens present in influenza vaccines induce a protective antibody response in vaccinated individuals. Mismatches between the B strain in the vaccine and the circulating strain occur in approximately 5 out of every 10 influenza seasons.[11] The CDC has estimated that in a season where there is a B strain mismatch, availability of QIV could have reduced annual influenza cases (range: 2200 to 970,000), hospitalisations (range: 14 to 8200), and deaths (range: 1 to 485) in the US.[13] QIV vaccines, inclusive of representative strains from both type B lineages, are being developed to reduce the potential public health burden of type B influenza morbidity and mortality in years where significant B strain mismatch may occur with TIVs.

Guidance

The QIV clinical development plan was discussed at two meetings with TGA held on 9 May 2013 and 27 May 2015. The plan was developed to be generally consistent with the TGA adopted European guidelines: CPMP/BWP/214/96 Harmonisation of Requirements for Influenza Vaccines and the EMEA/CHMP/VWP/164653/2005 Guideline on Clinical Evaluation of New Vaccines.

[9] Beyer W, et al., Protection against influenza after annually repeated vaccination: a meta-analysis of serologic and field studies. Arch Intern Med. 1999;159(2):182-8.
[10] Rota A, et al., Cocirculation of two distinct evolutionary lineages of influenza type B virus since 1983. Virology 1990 Mar; 175(1):59-68.
[11] Belshe, R. The need for quadrivalent vaccine against seasonal influenza. Vaccine 2010 Sep 7; 28 Suppl 4: D45-53.
[12] Ambrose C, et al., The rationale for quadrivalent influenza vaccines. Hum Vaccin Immunother 2012 Jan; 8(1):81-8.
[13] Reed C, et al., Public health impact of including two lineages of influenza B in a quadrivalent seasonal influenza vaccine. Vaccine 2012 Mar 2; 30(11): 1993 8.

In addition, the clinical development plan has been informed by the draft guidance of the European Medicine's Agency: EMA/CHMP/VWP/457259/2014 - *Committee for Medicinal Products for Human Use Guideline on influenza vaccines: Nonclinical and clinical module (25 July 2014),* although not yet effective in Europe[14], nor adopted by the TGA.

Contents of the clinical dossier

The submission contained the following clinical information:

- A pivotal Phase III randomised, multicentre, double blinded study (Study CSLCT-QIV-13-01) to evaluate the immunogenicity and safety of the sponsor QIV in comparison with the 2014 to 2015 Northern Hemisphere sponsor TIV (TIV-1) formulation and a TIV containing the alternate B-strain (TIV-2) in adults ≥ 18 years of age.
- Supportive studies of the trivalent influenza vaccine demonstrating clinical lot-to-lot consistency (Study CSLCT-FLU-05-09) and efficacy (Study CSLCT-USF-06-28).
- Supporting data for the Validation of the Haemagglutination Inhibition (HAI) Test for Titrating Influenza A and B Specific Antibodies for the 2 x A influenza strains and 2 x B strains included in this QIV.
- A Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety as well as Literature references.

Paediatric data

No paediatric data was submitted.

Good clinical practice

The clinical studies in this application complied with CPMP/ICH/135/95, an internationally accepted standard for the design, conduct, recording and reporting of clinical trials.[15] Ethical and scientific standards of the clinical studies complied with guidance documents of the International Conference on Harmonisation (ICH), the US FDA, and the TGA. The designs of the studies in this submission are consistent with recommendations from the US FDA Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines, May 2007 (CBER 2007). Furthermore, the designs of the adult QIV study and/or the presentation of results in this submission are also generally consistent with the EU 'Guideline on Clinical Evaluation of New Vaccines' (EMEA/CHMP/VWP/164653/2005; CHMP, 2006), and 'Note for Guidance on Harmonisation of Requirements for Influenza Vaccines' (CPMP/BWP/214/96; CPMP, 1997). Additionally, the adult QIV study and plans for future paediatric QIV studies are informed by the CHMP/VWP/457259/2014 Guideline on influenza vaccines Non-clinical and clinical module (draft), which accepts demonstration of non-inferior immunogenicity as a basis for marketing authorisation applications (MAA) in adults including the elderly.

Approvals to undertake the clinical studies were obtained from appropriately constituted institutional ethics committees/independent research boards, in accordance with the relevant national guidelines and regulations applicable.

Pharmacokinetics

This is not applicable to this application; no pharmacokinetic (PK) data is provided. The rationale is that PK studies are usually not required for vaccines.

[14] Since this evaluation was conducted, this guideline has become effective (1 February 2017).
[15] CPMP/ICH/135/95: Guideline for good clinical practice E6(R2).

Pharmacodynamics

Pharmacodynamics was not independently assessed.

Efficacy and safety data arising from the three studies is summarised under the respective subheadings below. Only one study provides immunogenicity data for the QIV.

Dosage selection for the pivotal studies

The dosage selection for the additional B strain immunogen in the QIV was based upon the standard used in the TIV that is 15 µg of HA per strain.

Efficacy

Studies providing efficacy data

The pivotal study CSLCT-QIV-13-01 is not a 'clinical efficacy' study, instead the immunogenicity data derived is used as a surrogate for clinical efficacy. This is a standard approach in influenza vaccine studies. In addition, the studies described in 'Section 7.2: Other studies' of Attachment 2 (Study CSLCT-FLU-05-09 and Study CSLCT-USF-06-28) are studies already reviewed by the TGA which demonstrate clinical lot-to-lot consistency and efficacy of Seqirus TIV and the immunogenicity study comparing QIV to two TIV comparators. An abridged review of both is provided in Attachment 2 as relevant only to this application.

Evaluator's conclusions on efficacy

The QIV has demonstrable immunogenicity in a US population of adults aged ≥ 18 years, based on the non-inferiority (for the 8 co-primary endpoints of HAI Geometric mean titres (GMT) and seroconversion rates (SCR)) of the four strains included in QIV, compared to two TIV formulations, and superiority for the QIV B strains not included in each of the two TIV comparator formulations. Non-inferiority and superiority (according to the study defined criteria for different strains and study vaccines) were also met for both the serological endpoints of haemagglutination inhibition (HI) GMT and SCR in the two age cohorts (adults aged 18 to 64 years and ≥ 65 years). Additional descriptive secondary immunogenicity endpoints including percentage with an HAI titre ≥ 40, SCRs and Geometric Mean Fold increases (GMFIs) by study vaccine and age cohort were analysed. In general, results were similar between different study vaccines within each age cohort for A strain results, and when the vaccine-included B strains were matched. Post-vaccination seroprotection rates for the A strains were very high (≥ 95%) and similar in both age cohorts. For the B strains post-vaccination seroprotection rates for subjects in the older age cohort (≥ 65 years of age) were lower than those in the 18 to 64 years of age cohort, even when the B strains were matched. Seroconversion rates in the overall study population of adults ≥ 18 years were generally in the range of 30 to 40% for both A strains and vaccine matched B strains. However, SCRs for subjects in the older age cohort ≥ 65 years were lower than the younger age cohort for all strains, even when the B strains were matched. One of the explanations for this is this is a study population that have had high rates of influenza vaccination in the previous 12 months. This pivotal study for QIV was not powered for clinical efficacy and at best, it is anticipated that clinical efficacy of QIV will be similar to that demonstrated for TIV for vaccine included and matched strains (around 60%).

Safety

Studies providing safety data

One key study, Study CSLCT-QIV-13-01 provided evaluable safety data for the QIV. The other two supporting studies (mentioned above) did not utilise the QIV and as such the clinical evaluator has opted to describe the safety data for these briefly (see Attachment 2 for further details).

Patient exposure

1721 of 1741 QIV recipients were included in the safety analysis.

Safety issues with the potential for major regulatory impact

No safety issues were revealed.

Postmarketing data

Not applicable for this submission.

Evaluator's conclusions on safety

In Study CSLCT-QIV-13-01, the safety profile of QIV in adults and older adults is generally similar to that observed for TIV-1 and TIV-2 vaccines. Solicited local and systemic reactogenicity was more frequent in adults 18 to 64 years of age compared to adults aged ≥ 65 years. Overall, the clinical evaluator thinks that QIV has a clinically acceptable safety and tolerability profile in adults ≥ 18 years at least in the relatively small number of patients enrolled in this study exposed to single dose QIV.

First round benefit-risk assessment

First round assessment of benefits

The benefits of Afluria Quad in the proposed usages are favourable as the QIV provides better coverage of the influenza B strains than the TIV. QIV was immunogenic with a safety profile similar to trivalent inactivated influenza vaccines in general, and to the specific TIV comparators used in the pivotal efficacy study. Moreover, the inclusion of both B strains will overcome the problem of poor predictions of which B strain is likely to circulate, this has been problematic over the last few years and has led to misalignment of the B strain in the recommended TIV with what was the circulating strain.

First round assessment of risks

The risks of Afluria Quad in the proposed usage are:

- there is a paucity of data in subjects of Asian ethnicity and this is relevant to the Australian population;
- there is a paucity of data in subjects of Australian indigenous ethnicity and this is relevant to the Australian population;
- the average age of the subjects enrolled was 58.3 (± 18) years, and although 29% of the cohort in total were aged 18 to 49 years, this suggests a relative paucity of patients in the much younger age group, specifically 18 to 30 years. As the reactogenicity

profile appears slightly worse in the younger age group overall, it will be important to gather further specific information on local and solicited vaccine-related adverse events (AE) in the much younger age group once QIV receives authorisation. The risk management plan (RMP) should specifically gather information in both the younger age group receiving the QIV as well as in those of ethnicity not represented in the pivotal study;

- there is no data on the immunogenicity and safety profile in immunocompromised patients as such patients were specifically excluded from participation;
- no clinical efficacy data provided, immunogenicity data is used as a surrogate for clinical efficacy.

These issues were included in the Clinical and RMP questions to the sponsor, to which the sponsor provided a response. Please refer to the sections 'Second round evaluation of clinical data submitted in response to questions' (Attachment 2) and 'Reconciliation of issues outlined in the RMP report' (below).

First round assessment of benefit-risk balance

The benefit-risk balance of Afluria Quad, given the proposed usages, is favourable.

First round recommendation regarding authorisation

The clinical evaluator recommends authorisation of Afluria Quad.

Clinical questions

The clinical evaluator had no questions pertaining to pharmacokinetics, pharmacodynamics or clinical safety. Questions regarding clinical efficacy are listed below.

Efficacy

1. What are the post-vaccination seroprotection rates for subjects over the age of 75 years for the B strains?
2. Do you have any explanation for why the seroprotection rates for B/Yamagata strain in adults aged ≥ 65 years was lower than for the B/Victoria lineage?

Second round evaluation of clinical data submitted in response to questions

For details of the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Afluria Quad in the proposed usage are unchanged from those identified in the First round assessment of benefits.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of Afluria Quad in the proposed usage are unchanged from those identified in the First round assessment on risks.

Second round assessment of benefit-risk balance

The benefit-risk balance of Afluria Quad, given the proposed usage, remains favourable.

Second round recommendation regarding authorisation

The clinical advisor recommends authorisation of Afluria Quad.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP) Version 1.0 (dated 25 September 2015, Data Lock Point 15 August 2015) and Australian-specific annex (ASA) Version 1.0 (dated 6 November 2015) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns in RMP Version 1.0 which are shown in Table 1 below.

Table 1. Sponsor's summary of ongoing safety concerns from RMP Version 1.0

Important identified risks	Hypersensitivity (anaphylaxis)
Important potential risks	Encephalomyelitis Seizures/convulsions Guillian-Barré syndrome Transverse myelitis Optic neuritis Bell's palsy Serum sickness
Missing information	Use in children < 18 years Exposure and safety in pregnancy

Pharmacovigilance plan

The sponsor proposed routine and additional pharmacovigilance activities for important identified and potential risks and missing information in RMP Version 1.0. These are shown below in Table 2.

Table 2. Sponsor's proposed routine and additional pharmacovigilance activities

Study/activity type	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of reports[1]
Routine pharmacovigilance ISCRs, PSURs/DSURs monitoring safety profile, safety signal detection and evaluation	To collect all AE reports and monitor these, along with other sources of safety information to detect and changes in the safety profile over time	All	Planned To be implemented when the QIV receives MAA	PSUR to be submitted as per regulatory requirement Signal detection activities will be conducted as defined in the sponsor signal detection SOP
Postmarketing surveillance of the QIV exposure in pregnancy and pregnancy outcomes	To collect the missing information of exposure of the QIV in pregnant women	Exposure and safety of the QIV in pregnancy (missing information)	To be planned and implemented when MAA is obtained for the QIV	ASR from pregnancy safety surveillance and final safety report from the pregnancy safety surveillance

ISCR = Individual Case Safety Report; PSUR = Periodic Safety Update Report; DSUR = Developmental Safety Update Report; MAA = Marketing Authorisation Approval; SOP = Standard Operating Procedure; ASR = Annual Safety Report. 1) Refers to interim or final reports (planned or actual).

Risk minimisation activities

Only routine risk minimisation activities are proposed for all safety concerns in Australia.

Reconciliation of issues outlined in the RMP report

Table 3 summarises the TGA's first round evaluation of the RMP, the sponsor's responses to issues raised by TGA the in the evaluation of the sponsor's responses.

Table 3. Reconciliation of issues outlined in the RMP report.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
Safety considerations may be raised by the nonclinical and clinical evaluators through consolidated TGA questions for the sponsor and/or the	*The nonclinical evaluation report suggests addition of 'No embryofetal development study has been conducted with Afluria Quad' to the precautions section of the PI. We accept TGA's recommendation and have added this statement to the PI provided with this response.* *The clinical evaluation report provided no recommendations related to safety.*	The sponsor's response has been noted.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
clinical evaluation report. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.		
It is expected that any subsequent versions of the RMP/ASA or RMP/ASA updates for the Afluria Quad contain relevant safety information from the RMP for the Fluvax TIV. The same applies to the proposed PI and CMI documents.	*The sponsor commit to providing an updated RMP and ASA with relevant information from the RMP for the trivalent vaccine. The updated RMP and ASA will be submitted to the TGA after the conclusion of evaluation.*	This is considered acceptable in the context of this application.
Due to its importance in this case, the sponsor should provide add 'Off-label use' as a separate Important Potential Risk to be addressed with additional risk minimisation activities.	*The sponsor commits to include off-label use in children 5 to 17 years of age as an important Potential Risk in an updated RMP. In addition, the sponsor commits to providing additional risk minimisation measures and a proposal to evaluate the effectiveness of such measure/s (as outlined in the sponsor's response to questions Q.16 and Q.17) until such time that an authorised indication of Afluria Quad for use in this age group has been obtained.* *The sponsor believes that the proposed additional risk minimisation measures in*	This is considered acceptable in the context of this application.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	children under 18 years are sufficient and will be continued to ensure the vaccine is not used in this age group.	
The sponsor should provide a summary of long-term safety with this product, or in the absence of this add 'long-term safety' as a missing information item.	*The sponsor does not agree that 'long term safety' should be added to the RMP as missing information.* *In Study CSLCT-QIV-13-01, serious adverse events (SAE) and protocol defined adverse events of special interests (AESI) relating to influenza vaccines were monitored for 180 days (6 months). Six-month follow up of safety data is generally considered a measure of long-term safety in clinical trials, especially for a seasonal product such as influenza vaccine.* *The sponsor commits to providing a summary of clinical trial SAEs and AESIs in an updated RMP.* *It should also be noted that post-marketing adverse events associated with use of Fluvax trivalent (TIV) are listed in the PI of Afluria Quad. Whilst they are not adverse events representing long-term safety, they indicate rare adverse events that might not have been possible to detect in the clinical trial setting due to limitation of the study sample size.*	This is considered acceptable in the context of this application.
'Use in non-Caucasians' should be added as a Missing Information item.	*The sponsor does not agree that 'Use in Non-Caucasians' should be added as missing information in the RMP.* *In Study CSLCT-QIV-13-01, of the overall adult Afluria Quad safety population (n = 1721), 304 of the study subjects were Non-Caucasians (304/1721, 17.7%). There was no difference in safety profile between Caucasian and non-Caucasian subjects observed in this study, and no biological reason to believe that non-Caucasians would be likely to experience different safety outcomes following influenza vaccination.*	This is considered acceptable in the context of this application.
The sponsor should provide information on whether the manufacturing process or the excipients have changed when compared to the currently approved Fluvax trivalent vaccine, that is,	*The proposed chemistry, manufacture, and control for Afluria Quad is the same as the currently approved manufacturing process for Fluvax TIV with the exception that the Afluria Quad vaccine contains four influenza vaccine strains in the formulation whereas Fluvax trivalent contains three. The HA content of the final Afluria Quad vaccine is therefore 60 µg HA per 0.5 mL whereas the current approved Fluvax TIV is 45 µg HA per 0.5 mL. Afluria Quad is formulated in an isotonic phosphate-buffered saline that has the same composition used to*	The sponsor's response has been noted.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
whether there is a difference in safety data due to factors other than composition of influenza strains.	*formulate Fluvax TIV. Due to the common manufacturing process, the excipients in the two products are also identical.*	
The sponsor should outline how the sponsor plans to measure the occurrence of off-label use (including active case finding) for this product.	*According to the EMA's Good Pharmacovigilance Practices Guidance (Module VI, Revision 1.0), there is no legal requirement to record a report of off-label use with no adverse events in the Marketing Authorisation Holder's (MAH) safety database for the collection of ICSR nor is there a requirement to submit ICSRs of off label use if not linked to a suspected adverse drug reaction (ADR). However, the sponsor's collect individual cases of off-label use (that is, use in an unauthorised indication) as ICSRs regardless of its association with ADR. Reports of off-label use are actively followed up in the exactly the same manner as for ICSRs. They are also included in the routine pharmacovigilance activities such as signal detection/evaluation, monitoring of benefit risk, and production of PSURs.* *The sponsor commits to providing a refresher pharmacovigilance (adverse event reporting) training to employees in the areas of medical information enquires, customer's complaint and sales/marketing on the requirement of reporting off-label use of Afluria Quad in children 5 through 17 years prior to the product being launched in Australia. This training will be repeated as required until such time that the sponsor has obtained authorised indication of Afluria Quad for use in this age group. Other information sources available to the MAH will also be monitored for identification of off-label use Afluria Quad in children 5 through 17 years.* *In addition to the above routine pharmacovigilance activities, the sponsor commits to distributing a Direct Healthcare Professional Communication (DHPC) letter which emphasizes the following message:* *Afluria Quad is indicated ONLY for adults 18 years and older* *If HCP has become aware of any off-label use of this product in clinical practice, not limited to his/her own clinic, to report this to the sponsor's adverse event reporting centre (email, fax and contact details to be provided in the DHCP letter).*	Legal requirements constitute minimum requirements. Each application is assessed individually and additional conditions may be requested by the regulator. Off-label use is a significant concern with this product. Medical practitioners currently associate Fluvax with an age group of 5 years and above. To assess off-label use, the sponsor should propose an additional pharmacovigilance activity to estimate the degree of off-label use.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
Given the limited amount of data available, the sponsor should propose an additional pharmacovigilance activity that evaluates safety data from the population group aged 18 to 30 years of age.	*The sponsor does not consider an additional pharmacovigilance activity is required for the 18 to 30 years age sub-group.* *Study CSLCT-QIV-13-01 was designed to have age sub-groups that were proportionally reflective of the age sub-groups for which influenza vaccine is generally utilised in Australia, or other countries where there are elderly age indications, and risk-based recommendations for adults 18 through 59 years inclusive. These recommendations result in highest influenza vaccination rates in adults 65 years and older, and adults 50 through 64 years inclusive, which is the adult age group with higher frequencies of co-morbidities. The study design included a minimum target of at least 30% of subjects ≥ 75 years (for subjects ≥ 65 years), and no greater than 60% in either adult age subgroup 18 to 49 years inclusive, or 50 to 64 years inclusive (for subjects 18 to 64 years inclusive). In this study, the 18 to 30 years old safety population for the QIV treatment group is 198/496 (40%) of the adult 18 to 49 years age sub-group and 198/854 (23%) of the adult 18 to 64 years inclusive age sub-group, respectively.* *It is also noted that there have not been any safety signals for Fluvax TIV specific to this age-group from historical Fluvax TIV data.* *Given the representative age distribution of the QIV adult study safety population relative to the population in which the vaccine will be utilised in Australia, and that there are already a considerable number of subjects aged 18 to 30 years included in the QIV clinical safety assessment population, the sponsor believes that routine pharmacovigilance and risk minimisation activities as specified in the RMP are sufficient.*	This is considered acceptable in the context of this application.
Given the limited amount of data available, the sponsor should propose an additional pharmacovigilance activity that evaluates safety data from the Non-Caucasian population (in	*The sponsor does not propose an additional pharmacovigilance activity based on racial or ethnic subsets.* *Given that the clinical and post-marketing experience with the sponsor's TIV has not previously indicated any race or ethnicity linked safety signals in adults following extensive and prolonged use of the product in Australia, and that the same method of manufacture is used for Afluria Quad as for Fluvax TIV, it is considered that routine pharmacovigilance activities and*	The sponsor's response has been noted.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
particular the Asian and Indigenous population).	*safety signal detection as proposed in the RMP should be appropriate.* *In a previous Fluvax TIV study of adults ≥ 18 to < 64 years (CSLCT-USF-06-28 (NCT00562484)), over 900 Asian, Pacific Islander, and Indigenous subjects were administered Fluvax TIV, and these groups were not observed to have a different reactogenicity profile to the safety population as a whole.* *In reference to the response to Q.5, it is also noted that in Study CSLCT-QIV-13-01 there were 304 Non-Caucasians included in the QIV safety population (304/1721, 17.7%) of study subjects in the overall adult QIV safety population. No difference in safety profile between Caucasian and non-Caucasian subjects were observed in this study.*	
It is noted that the RMP for Fluvax TIV contains the following study which should also be added to the RMP for Fluvax QIV: Post-Authorisation Safety Study (PASS): Observational Influenza Vaccine Active Surveillance Study: A Phase IV Prospective Multi-Centre Cohort Study to Evaluate the Reactogenicity of the sponsor's Influenza Virus Vaccine (Category 2).	*This Post-Authorisation Safety Study for Fluvax TIV is currently being conducted in accordance with the EU guideline Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU (EMA/PRAC/222346/2014, effective 15 April 2014). The sponsor will provide the reference to the above study in the RMP for Afluria Quad.*	The sponsor's response has been noted.
The sponsor should state whether the Fluvax trivalent vaccine is proposed to be marketed alongside the Afluria Quad in Australia, as this has implications on	*Following the registration of Afluria Quad, the sponsor will no longer supply Fluvax trivalent to the Australian market. Within an influenza season, only one vaccine, either Fluvax trivalent or Afluria Quad vaccine will be supplied to the market by the sponsor.*	The sponsor's response has been noted.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
the risk minimisation activities that need to be conducted.		
The sponsor should state which device is intended to be used for the Afluria Quad in Australia (that is, pre-filled syringe and/or PharmaJet Stratis jet injector (as used in the US).	*Only the pre-filled syringe presentation is intended to be registered for Afluria Quad and will be used in Australia. The PharmaJet Stratis jet injector will not be registered and will not be used for administration of Afluria Quad in Australia.*	The sponsor's response has been noted.
Assuming the same device as in the currently approved Fluvax TIV is used, the sponsor should provide a summary of the post-market experience with device failure with that device and its effects (for example underdosing).	*As only the pre-filled syringe presentation will be registered for Afluria Quad and used in* *Australia, post-market experience with device failure is not relevant to the pre-filled syringe presentation.*	The sponsor's response has been noted.
Assuming, the PharmaJet Stratis jet injector device is used, the sponsor should provide a summary of the post-market experience with device failure with that device and its effects (for example underdosing).	*Only the pre-filled syringe presentation is will be registered and used in Australia.*	The sponsor's response has been noted.
The sponsor should state how they propose to address the issue of confusion between the Fluvax TIV and the Afluria Quad and their indications. Additional risk	*As stated above, within an influenza season, only one vaccine, either Fluvax TIV or Afluria Quad will be supplied to the market by the sponsor. Appropriate educational materials will be provided to educate Australian health professionals about the indications of Afluria Quad vaccine. These materials outlined in Q.17 will be developed following registration and prior to the anticipated launch of the vaccine in the Australian market. Once prepared, these*	The sponsor's response has been noted. It is furthermore noted that the sponsor is already proposing an

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
minimisation activities would be needed to mitigate off-label use.	*materials can be made available to the TGA.*	extension of indication that would align the current indication of the TIV with the overall proposed indication of Afluria Quad. If approval for this extension of indication were given before supply of the Afluria Quad under the currently proposed indication, the age ranges would be aligned. However, if the application for the extension of indication were unsuccessful, or if the Quad were to be supplied with the currently proposed indication prior to an approval of an indication that aligns the age ranges, then the issue would have to be revisited by TGA and a different strategy may need to be proposed. In any case, the proposed actual materials (including

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
		package labelling) need to be provided to the TGA prior to supply. Furthermore, a different trade name for the Quad would be desirable, where the Quad indicated age range is a subset of the current Fluvax TIV indicated age range. (The same trade name would be acceptable, if the proposed indicated age range is identical or exceeds the currently indicated age range.)
The sponsor should propose a plan to sufficiently mitigate the risks of: Confusion with the Fluvax trivalent vaccine, potential leading to off-label use in children aged 5 to 17 years of age. This may be in the form of a Dear Health care provider Letter (DHCPL) and other communication items, as well as product labelling and packaging	*At a minimum the sponsor will commit to the following activities to communicate the age indication of Afluria Quad vaccine and minimise the risks of potential off-label use in children under 18 years of age:* *- The Afluria Quad vaccine age indication on the package labelling* *- A different colour label* *- A DHCPL* *- An electrostatic vaccine refrigerator sticker that clearly states the age indication of Fluvax quadrivalent vaccine* *- An A5 card that summarises the current Australian Technical Advisory Group's (ATAGI) recommendations for use of influenza vaccine by brand, age group and availability on the National Immunisation Program (NIP).*	This is considered acceptable in the context of this application. The description of the conduct of additional risk minimisation activities should be included in an updated ASA. The proposed actual materials (including package labelling) need to be provided

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
labelling.		to the TGA prior to supply.
For this submission, the sponsor should provide the TGA with the following details for agreement: All draft Australian additional risk minimisation activity materials; A clear distribution plan for Australia; and A clear plan to measure the effectiveness of the additional risk minimisation activities.	*Following registration the sponsor will commit to the following activities to communicate the age indication of Afluria Quad vaccine and monitor effectiveness of risk minimisation activities:* *A DHCPL mailed to all pharmacists, general practitioners and medical practices, during the month of March.* *An electrostatic vaccine refrigerator sticker that clearly states the age indication of Afluria Quad vaccine mailed to all medical practices and pharmacies during the month of March.* *An A5 card that summarises the current Australian Technical Advisory Group on Immunisation (ATAGI) recommendations for the use of influenza vaccine by brand, age group and availability on the National Immunisation Program (NIP) mailed to all general practitioners and pharmacists during the month of March.* *Market research after the influenza season to measure HCPs awareness of the Afluria Quad vaccine's age indication.* *The sponsor proposes that these activities continue each influenza season until Afluria Quad vaccine receives approval for a paediatric indication for children less than 18 years.*	This is considered acceptable in the context of this application. The description of the conduct of additional risk minimisation activities should be included in an updated ASA. The proposed actual materials (including package labelling) need to be provided to the TGA prior to supply.
There should be a boxed warning stating that this vaccine can only be used in patients over 18 years of age (similar to the warning in the Fluvax TIV PI).	*To minimise the risk of Afluria Quad being used in persons under the age of 18 years, the Afluria Quad PI has been revised to include a contraindication in this age group. Additionally the Afluria Quad cartons have been revised to include the statement 'For use in persons 18 years or older'. The label has also been updated to a different colour than Fluvax TIV and to include the statement 'For 18 years or older'. Additionally, the revised RMP will include additional communication activities including mail out of DHCPL, a sticker stating the age indication for Afluria Quad and an A5 card summarising the ATAGI recommendations.* *Whilst there is a boxed warning for Fluvax TIV stating that indicated for use only in persons aged 5 years and over, it is important to note that the development of Afluria Quad is based on*	This is considered acceptable in the context of this application for RMP purposes pending consideration by the Delegate.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	the findings of the scientific investigation into the root cause of the Southern Hemisphere 2010 paediatric febrile events. The scientific investigation identified that Fluvax TIV stimulates release of inflammatory cytokines and chemokines in adult and paediatric whole blood assays and in cell line assays which is mediated by degraded RNA transcripts delivered by a lipid vector).[3,16] With splitting conditions of 1.5% weight/volume (w/v) TDOC for the B strain RNA and lipid levels are reduced and in cell line assays inflammatory cytokine and chemokine responses are reduced. To determine whether this translated to a reduction in fever rates in children aged 5 to < 9 years following vaccination with Fluvax TIV a clinical study was conducted with Fluvax TIV manufactured with 1.5% w/v TDOC splitting conditions for the B strain. *Study CSLCT-USF-10-69 [NCT02212106] (as described in the Fluvax TIV RMP submitted to TGA 16 September 2015) is Phase IV, randomised, parallel-arm, descriptive safety and tolerability study (CSLCT-USF-10-69) which enrolled 402 children age 5 to < 9 years. The study compared Fluvax TIV manufactured with 1.5% w/v sodium taurodeoxycholate (TDOC) splitting conditions for the B strain with a US-licensed Quadrivalent Influenza Virus Vaccine (QIV; Fluzone Quadrivalent (Sanofi Pasteur)). The primary objective of the study was to evaluate the frequency and intensity of fever in healthy paediatric subjects 5 to < 9 years of age. The study enrolled 402 subjects randomized in a 3:1 allocation to receive Fluvax TIV (302 subjects) or comparator Quad; 100 subjects). Subjects received one or two study vaccinations (0.5ml dose) depending on their influenza vaccination history.* *The results of the study demonstrated that the overall fever rate and severe fever rate was comparable between the two vaccines, 8.2% and 2.1% respectively for Fluvax TIV and 9.2% and 4.1%, respectively for Comparator Quad. Related fever events occurred in 7.5% subjects vaccinated with Fluvax TIV and in 5.1% subjects vaccinated with Comparator QIV. Related severe fever events occurred in 1.7% of subjects vaccinated with Fluvax TIV; none occurred in*	

[16] Rockman et al., Evaluation of the bioactivity of influenza vaccine strains in vitro suggests that the introduction of new strains in the 2010 Southern Hemisphere Trivalent Influenza Vaccine is associated with adverse events. Vaccine; 32:30, p 3861-3868

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	subjects vaccinated with Comparator Quad. *The results of the study were compared to historical rates observed in previous paediatric clinical studies in children aged 5 to < 9 years vaccinated with Fluvax TIV. In this study the overall and severe fever rates were lower in children who were vaccinated with Fluvax TIV manufactured with 1.5% TDOC for splitting of the B strain.* *The results of the study provide some evidence to suggest that there may be an attenuation in the systemic reactogenicity profile for Fluvax TIV following the adjustment to B strain TDOC splitting concentrations. The study has provided data to inform the study design and supported the initiation of Afluria Quad paediatric clinical development. The manufacture of Afluria Quad with 1.5% w/v TDOC splitting conditions for the B strain may also attenuate the systemic reactogenicity profile.* *Therefore, the sponsor does not believe a boxed warning regarding use in children less than 18 years is warranted.*	
In the 'Precautions' section, a statement on the known information with regard to febrile seizures should be provided.	*The statement 'Administration of the 2010 Fluvax TIV was associated with increased rates of fever and febrile seizures, predominantly in children below the age of 5 years as compared to previous years.' has been added in the updated PI.*	This is considered acceptable in the context of this application for RMP purposes pending consideration by the Delegate.
In the 'Precautions' section, the PI should contain a statement that adrenaline should always be ready for immediate use.	*The statement 'Adrenaline should always be ready for immediate use whenever any injection is given.' has been added in the updated PI.*	This is considered acceptable in the context of this application for RMP purposes pending consideration by the Delegate.
In the 'Precautions' section, the PI should contain a statement with	*The statement 'If Guillain-Barré syndrome has occurred within 6 weeks of previous influenza vaccination, the decision to give Afluria Quad vaccine should be based on careful*	This is considered acceptable in the context of

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
regard to giving the vaccine to patients who had Guillain-Barré syndrome in the last 6 weeks.	*consideration of the potential benefits and risks.' has been added in the updated PI.*	this application for RMP purposes pending consideration by the Delegate.
In the 'Interactions' section the PI should contain a statement that if Fluvax vaccine were to be administered concurrently with other vaccines, separate syringes and a separate arm should be used.	*This statement is currently listed in the Dosage and Administration section of the PI which the sponsor believes to be the most appropriate placement of this statement as it relates to administration of the vaccine not an interaction.*	This is considered acceptable in the context of this application for RMP purposes pending consideration by the Delegate.
In the 'Contraindications' section, the PI should contain 'patients younger than 18 years of age' as a contraindication.	*The statement 'Afluria Quad is contraindicated in children < 18 years because the safety and efficacy in this age group has not been established' has been added in the updated PI.*	This is considered acceptable in the context of this application for RMP purposes pending consideration by the Delegate.
In the 'Dosage and Administration' section, the PI should include a statement that administration should occur by a health care practitioner in an appropriate setting with an appropriate post-vaccination observation period.	*The statement 'Afluria Quad vaccine should be administered by a health care practitioner in an appropriate setting with an appropriate post-vaccination observation period.' has been added in the updated PI.*	This is considered acceptable in the context of this application for RMP purposes pending consideration by the Delegate.
It is recommended to the Delegate that the draft consumer medicines information (CMI) document be	*The consumer medicines information will be updated for consistency with the recommendations in the product information.* *In reviewing the revised Product Information for Afluria Quad, an inconsistency in the Post*	This is considered acceptable in the context of this application for RMP

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
revised to accommodate the changes made to the product information document.	*marketing experience of the Adverse Effects section was identified. Under Nervous System Disorders convulsions also refers to (including febrile convulsions). The reference to febrile convulsions relates to children under the age of 5 years so is not relevant to the 18 years or older indication sought for Afluria Quad. Therefore the sponsor proposes to remove (including febrile convulsions) from the Post marketing experience of the Adverse Effects section the updated Afluria Quad PI.*	purposes pending consideration by the Delegate.

Summary of recommendations

The RMP evaluator identified the following recommendations and/or outstanding issues:

1. To assess off-label use, the sponsor should propose an additional pharmacovigilance activity to estimate the degree of off-label use (See Recommendation 7 in Table 3 above).
2. A different trade name for the Quad would be desirable, where the Quad indicated age range is a subset of the current Fluvax TIV indicated age range (See recommendation 15 in Table 3 above).
3. The description of the conduct of additional risk minimisation activities should be included in an updated ASA. The proposed actual materials (including package labelling) need to be provided to the TGA prior to supply (See Recommendations 15, 16 and 17 in Table 3 above).

Request for ACSOV advice

The RMP evaluator had questions for which the Australian Committee on the Safety of Vaccines (ACSOV) provided the following advice:

1. *Can the committee comment on the need for additional risk minimisation activities or other measures to mitigate the risk of confusion between Fluvax TIV and QIV [Quad], and to mitigate off-label use?*

The committee noted that a contraindication for Fluvax TIV is use in children under the age of five years, while a contraindication for Fluvax Quad [Afluria Quad] is use in children (under the age of 18 years). A key point of the sponsor's risk minimisation activities should be to address this source of possible confusion between Fluvax TIV and Fluvax Quad [Afluria Quad].

The committee advised that the vaccine's name and labelling will be critical to minimising risks of confusion between Fluvax Quad [Afluria Quad] and Fluvax TIV, and between Fluvax Quad [Afluria Quad] and other QIV. The main consequence of confusion will be inadvertent off-label use in children.

The committee advised against the approval of the proposed name Fluvax Quad [Afluria Quad]. Risk minimisation activities by public health bodies and the sponsor since 2010 have emphasised the message 'Fluvax is not to be used in children under five years of age'; these activities make no mention of the valency of the vaccine. The relevant message for Fluvax Quad [Afluria Quad] will be 'do not use in children at all' (that is, only for adults), which initially will be less memorable than the Fluvax TIV message that has been in place

for several seasons. This creates a real potential that Fluvax Quad [Afluria Quad] will be used unintentionally off-label in children aged 5 to 18 years. This potential for use of Fluvax Quad [Afluria Quad] in children aged 5 to 18 years exists whether or not Fluvax TIV is supplied in the same influenza season and is present in the same refrigerator in a clinic.

The committee noted that Fluvax Quad [Afluria Quad] has not been administered to children, and its safety and efficacy in children is unknown. While a paediatric study is planned in children aged 5 to 18 years, the results of such a study may not be available when Fluvax Quad [Afluria Quad] first becomes available in Australia. This will be a time of elevated risk of off-label use.

As a minimum, the features of Fluvax Quad [Afluria Quad] that are the key differences from Fluvax TIV should be clearly highlighted on the labelling of the quadrivalent vaccine, including the age group of patients in which the vaccine can be used.

The effectiveness of routine risk minimisation (PI and labelling) to ensure usage only in the indicated population will need to be confirmed through routine signal detection and review in every PSUR.

The committee further commented that the trade name 'Fluvax' is effectively a contraction of 'influenza vaccine', which has/could lead to the name, 'Fluvax' being misunderstood as a generic term for 'influenza vaccine' and for 'Fluvax' to be seen as interchangeable with other influenza vaccines. This is not the case.

The committee agreed with the TGA evaluator's request to the sponsor to provide information on whether the manufacturing process or the excipients have changed when compared to Fluvax TIV, that is, whether there may be a difference in safety profile due to factors other than the quantity, concentration and composition of influenza antigens.

2. *Can the committee comment on the need to conduct an additional pharmacovigilance activity to investigate and evaluate the likely degree of off-label use of Fluvax Quad [Afluria Quad]?*

The committee noted the size of the exposed populations for recently approved QIVs. For Fluarix Tetra, a total of 4228 individuals were exposed to at least one dose of the vaccine in Phase III studies.[17] For FluQuadri, clinical safety was addressed in three studies, involving 190 adults, 220 adults aged over 65 years of age, and 2339 children (6 months to 8 years of age).[18] By comparison, there were only 1721 adult subjects in the population who received one dose of Fluvax Quad [Afluria Quad]. Further, the Fluvax Quad [Afluria Quad] trial was conducted in a single influenza season while trials for other QIVs were across more than one influenza season.

In addition to a smaller total number of patients, the RMP provided only limited information on safety data for Fluvax Quad [Afluria Quad] in special populations. Use in pregnant women has been identified as missing data, which is unfortunate given that pregnant women are considered to be more at risk of complications from influenza and are therefore targeted for vaccination via public health campaigns. Patients with comorbidities such as asthma were excluded from the clinical trial; this information is not stated in the PI.

Due to the limited data available, the committee advised that additional clinical trials to address knowledge gaps, including safety in Aboriginal and Torres Strait Islander people, should be included as additional activities in the pharmacovigilance plan.

[17] AusPAR for Fluarix Tetra influenza virus haemagglutinin inactivated split influenza vaccine GlaxoSmithKline Australia Pty Ltd PM-2012-02287-3-2
[18] AusPAR for FluQuadri influenza virus haemagglutinin H1N1, H3N2, B Victoria lineage, B Yamagata lineage Sanofi-Aventis Australia Pty Ltd PM-2013-02401-1-2

Ideally, population-based studies using data linkages from immunisation registers should be undertaken to establish the prevalence of off-label use. Until such studies can be undertaken, extraction of data from primary care prescribing software or other post market surveillance data sets would be useful, as long as the various quadrivalent vaccines are differentiated in these databases.

VI. Overall conclusion and risk/benefit assessment

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

Quality

The quality evaluators raised concerns in relation to quality aspects of this product, relating to:

1. *Quantification and control of impurities*
2. *Risk of adventitious agents*
3. *Aggregates in drug substance and drug product*
4. *Colour of the syringe labelling* prior to Milestone 7.
5. *Potency estimation differences between target, release and clinical trial lots*
6. *Lack of a quantitative methodology for virus particles*
7. *Annual SRD qualification*

The sponsor responded to these issues as part of the ACMP process and they were later resolved through consultation with TGA. Please refer to the outcomes section at the end of this document.

Batch release conditions of registration for clinical Delegate: Should the product be approved, details of the specific requirements associated with batch release and testing will be forwarded to the Delegate prior to finalisation of administrative and registration activities.

Nonclinical

No nonclinical studies were submitted. The lack of studies was justified in the nonclinical overview on the basis of prior marketing experience with the TIV and clinical trial data for the QIV.

The Fluvax TIV is a grandfathered product. One embryofetal development study was conducted with Fluvax TIV. The study showed no effects on rat mating, fertility, and embryofetal or pup development. The registered QIVs Fluarix Tetra (GlaxoSmithKline) and FluQuadri have been assigned an Australian pregnancy category of B1.

At the pre-submission meeting the sponsor was advised that, although not essential for registration, an embryofetal development study with the QIV would provide additional assurance regarding safe use.

The reproductive toxicity study of the sponsor's TIV in female rats did not demonstrate any adverse effects on mating, fertility, embryo-foetal development and vaccine-related teratogenic effects. Each dose of the TIV contained 45 µg of HA, resulting in each dose being approximately 265 times the human dose on an mg/kg of bodyweight basis; equating to a dose approximately 200 times the human mg/kg dose for the QIV, taking

into consideration the additional HA content from the fourth influenza strain. As the sponsor's QIV formulation is based on the sponsor's TIV, with the exception of the additional B strain, it is expected to have a similar safety profile to that established for the TIV.

There are no nonclinical objections to registration of this QIV.

Clinical

The data for clinical evaluation includes the following three studies:

- One pivotal Phase III study (Study CSLCT-QIV-13-01);
- One clinical lot-to-lot consistency study (Study CSLCT-FLU-05-09) for the TIV;
- One efficacy study (Study CSLCT-USF-06-28) for the TIV.

The submission does not include paediatric efficacy and safety data, although paediatric studies are ongoing and/or planned that is, in Study CSLCT-QIV-13-02.

Pivotal study: Study CSLCT-QIV-13-01

This is a Phase III, multicentre, randomised, double-blinded study. The study was to evaluate the non-inferior immune response of the sponsor's QIV to that of the sponsor's TIV-1 and TIV-2 along with safety in adults aged ≥ 18 years. The study was conducted during the 2014 to 2015 Northern Hemisphere influenza season in healthy adults ≥ 18 years. Subjects were randomised to one of the 3 groups in a 2:1:1 ratio. The randomisation was stratified by age stratum (≥ 18 to 64 years and ≥ 65 years). This study is not a clinical efficacy study; instead the immunogenicity data derived is used as a surrogate for clinical efficacy.

Standard definitions of influenza vaccine 'immunogenicity', in terms of SCR, seroprotection rate (SPR), and geometric mean fold increase of the vaccine in influenza vaccine studies were used (see Attachment 2 for details). Bloods for immunogenicity assessments were collected from all subjects immediately before and at Visit 2. The primary objective was to demonstrate that vaccination with this QIV elicits an immune response that is not inferior to that of TIV containing the same strains as the US licensed 2014 to 2015 Seqirus influenza vaccine (Seqirus TIV-1), and the TIV containing the alternate B strain (Seqirus TIV-2) in adults aged ≥ 18 years. Secondary objectives were to demonstrate that:

- vaccination with the QIV elicits an immune response that is not inferior to that of TIV-1 and the TIV-2;
- the immunological superiority of the QIV compared to TIV-1 and TIV-2 for the B strain that is not included in each TIV vaccine separately; and
- to characterise the immunogenicity of QIV, TIV-1 and TIV-2.

Inclusion criteria: Healthy male or non-pregnant female aged ≥ 18 years; in good health, or in stable health status with no exclusionary medical or neuropsychiatric conditions, as determined by screening evaluation and a physical examination conducted no greater than 14 days prior to vaccination; Able to understand and comply with study requirements; if applicable, females of child-bearing potential must be abstinent or be willing to use a medically accepted contraceptive regimen for the duration of the On-study Period.

The details of the exclusion criteria are listed in Attachment 2.

The study vaccine is the inactivated, split-virion, thiomersal-free QIV administered as one 0.5 mL IM dose. Each 0.5 mL dose contains 15 µg HA from each of the following 4 strains

which were recommended by the FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) for the 2014 to 2015 influenza seasons in the US:

- 15 µg A/California/7/2009 (H1N1) pdm09-like virus;
- 15 µg A/Texas/50/2012 (H3N2)-like virus;
- 15 µg B/Massachusetts/2/2012-like virus (B/Yamagata lineage);
- 15 µg B/Brisbane/60/2008-like virus (B/Victoria lineage).

The comparator vaccines were:

Seqirus TIV-1 (Afluria): inactivated, split-virion, TIV, administered as one 0.5 mL IM dose. Each 0.5 mL dose contains 15 µg HA from each of the following 3 strains:

- 15 µg A/California/7/2009 (H1N1) pdm09-like virus;
- 15 µg A/Texas/50/2012 (H3N2)-like virus;
- 15 µg B/Massachusetts/2/2012-like virus (B/Yamagata lineage).

Seqirus TIV-2: inactivated, split virion, TIV, administered as one 0.5 mL IM dose. Each 0.5 mL dose contains 15 µg HA from each of the following 3 strains (two influenza A strains recommended for a TIV by the FDA VRBPAC for the 2014 to 2015 influenza season in the US and the alternate B strain to that recommended for TIV):

- 15 µg A/California/7/2009 (H1N1) pdm09-like virus;
- 15 µg A/Texas/50/2012 (H3N2)-like virus;
- 15 µg B/Brisbane/60/2008-like virus (B/Victoria lineage - alternate B strain).

The primary efficacy outcomes include immunogenicity at 21 days after vaccination by measuring HAI titres to the 4 strains. The non-inferiority of QIV compared to TIV-1, and to TIV-2 assessed for the co-primary endpoints of HI GMT and SCR for each virus strain:

- The GMT ratio for the A/H1N1 strain;
- The GMT ratio for the A/H3N2 strain;
- The GMT ratio for the B strain (Yamagata lineage);
- The GMT ratio for the B strain (Victoria lineage);
- The difference between the SCR for the A/H1N1 strain;
- The difference between the SCR for the A/H3N2 strain;
- The difference between the SCR for the B strain (Yamagata lineage);
- The difference between the SCR for the B strain (Victoria lineage).

The definitions of the full analysis set, per-protocol population, and evaluable population for immunogenicity analysis are described in Attachment 2. This study is powered to achieve 80% power to demonstrate non-inferiority in each age stratum over 8 co-primary endpoints, SCR for 4 strains, GMT for 4 strains using a one-sided alpha of 0.025 for each comparison. No adjustment for multiple endpoints was made. For comparisons of SCR a non-inferiority margin of 10% (TIV – QIV) will be employed. It is assumed that the SCR for all strains for TIV is 50% and that there is no difference between QIV and TIV. For comparison of GMT ratio a non-inferiority margin of 1.5 (TIV/QIV) will be employed. It is assumed that there is no difference between QIV and TIV (that is, a ratio of 1) and that the standard deviation of log (titre) is 1.4.

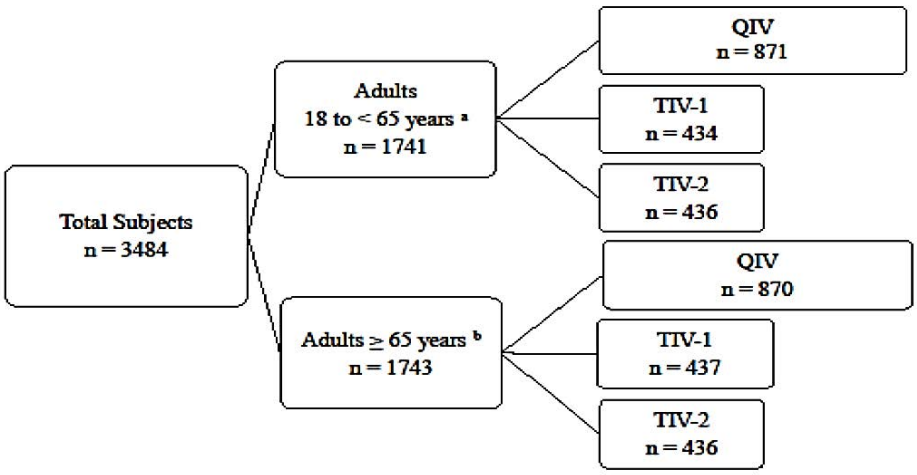
Overall 3304 evaluable subjects are required. Allowing for a 5% drop-out, 3480 subjects will be recruited (1740 per age stratum).

The difference in SCR (TIV – QIV) for each strain will be determined and presented with 95% CI. Non-inferiority concluded for each strain if the upper 95% confidence limit is < 10%. HAI titres will be log transformed and a General linear model (GLM) will be fitted with Day 21 log (titre) as the outcome variable and vaccine (TIV or QIV), site, age stratum and pre-vaccination titre as covariates. The least squares mean for TIV – QIV will be obtained from the model with 95% CIs. The point estimate and confidence limits will be exponentiated to obtain GMT ratio with 95% CIs. Non-inferiority concluded if upper 95% confidence limits are < 1.5. If all 8 co-primary endpoints result in a conclusion of non-inferiority then overall non-inferiority of QIV to TIV-1 and TIV-2 will be concluded. This assessment conducted overall (the primary endpoint) and by age stratum (a secondary endpoint).

In addition, to address secondary objectives, the superiority of QIV over TIV-1 and TIV-2 for the alternate B strain will be assessed using GMT ratio (QIV/TIV) and difference in SCR (QIV – TIV). Point estimates and 95% CIs will be obtained as described for the primary endpoint. Superiority will be declared if the lower 95% confidence interval (CI) for the difference in SCR (QIV – TIV) is 0 and the lower 95% CI for the GMT ratio (QIV/TIV) is > 1 for both B strains. GMT will be summarised at Day 1 and Day 21 by treatment group overall and by age stratum. GMFI will be determined for each strain for each treatment group as the GMT ratio of Day 21/Day 1. The % of subjects who are seroprotected (HAI titre ≥ 40 at Day 1 and Day 21) will be summarised by treatment group overall and by age stratum.

A total of 3484 subjects were enrolled: 1741 in the 18 to 65 age group and 1743 in the ≥ 65 age group.

Figure 1. Study CSLCT-QIV-13-01 - Subject stratification and treatment allocation schema (Actual study numbers – Full analysis set)



a) Adults < 65 years of age, a maximum of 60% in one subgroup (18 to < 50 years or 50 to <65 years). b) Adults ≥ 65 years of age, a minimum of 30% in the > 75 year age subgroup.

Table 4. Study CSLCT-QIV-13-01 Subject disposition

	CSL QIV n	(%)	CSL TIV-1 n	(%)	CSL TIV-2 n	(%)	Overall n	(%)
Reasons for discontinuation								
Adverse Event(s)	0		0		0		0	
Protocol Violation	0		0		0		0	
Lost to Follow-Up	46	(2.6)	18	(2.1)	18	(2.1)	82	(2.4)
Withdrawal by Subject	2	(0.1)	0		2	(0.2)	4	(0.1)
Study Terminated by Sponsor	0		0		0		0	
Physician Decision	0		0		0		0	
Death	5	(0.3)	0		1	(0.1)	6	(0.2)
Other	2	(0.1)	1	(0.1)	1	(0.1)	4	(0.1)

bioCSL PTY LTD: CSLCT-QIV-13-01/CIL-MJ/FINAL FOLLOW-UP(DATA TRANSFER=08MAY2015: DATA LOCKED=11MAY2015)/EOS01P.SAS
Produced: 27 May 2015, 13:04
Source: Listing 16.2.1.1
Notes: [1] Table presents number and percentage of subjects (n (%))
[2] Percentages are based on the number of subjects in the FAS in each group
[3] ^ Percentages for the reason for screen failure are based on the number of screen failures in each group

Table 5. Study CSLCT-QIV-13-01 Analysis populations

Analysis Populations	bioCSL QIV (n = 1741)	bioCSL TIV-1 (n = 871)	bioCSL TIV-2 (n = 872)	Overall (n = 3484)
Full Analysis Population, n (%)	1741	871	872	3484
Safety Population, n (%)	1721 (98.9%)	864 (99.2%)	864 (99.1%)	3449 (99.0%)
Evaluable Population, n (%)	1704 (97.9%)	857 (98.4%)	854 (97.9%)	3415 (98.0%)
Per-Protocol Population, n (%)	1691 (97.1%)	854 (98.0%)	850 (97.5%)	3395 (97.4%)

Table 6. Study CSLCT-QIV-13-01 Baseline characteristics

	bioCSL QIV N=1741	bioCSL TIV-1 N=871	bioCSL TIV-2 N=872	bioCSL TIV (pooled) N=1743	Overall N=3484
Age (years)					
Mean ± SD	58.3 ± 18.10	58.2 ± 18.10	58.3 ± 17.89	58.2 ± 17.99	58.3 ± 18.04
Age Group (%)					
18 to 49 years	29.3	29.3	29.2	29.3	29.3
50 to 64 years	20.7	20.6	20.8	20.7	20.7
65 to 74 years	31.1	31.1	31.0	31.0	31.1
≥ 75 years	18.9	19.1	19.0	19.0	19.0
Gender (%)					
Male	44.2	41.3	41.5	41.4	42.8
Female	55.8	58.7	58.5	58.6	57.2
Ethnicity (%)					
Hispanic or Latino	4.8	6.5	3.6	5.0	4.9
Not Hispanic or Latino	94.9	93.3	96.2	94.8	94.9
Not Reported	0.2	0.1	0.2	0.2	0.2
Race (%)					
White	82.0	82.5	82.8	82.7	82.3
Black or African American	16.3	15.0	15.5	15.3	15.8
Asian	0.7	0.8	0.5	0.6	0.7
Other	0.6	0.7	0.7	0.7	0.7
Native Hawaiian or Pacific Islander	0.1	0.5	0	0.2	0.2
Weight (kg)					
Mean ± SD	85.48 ± 21.45	85.58 ± 21.30	85.08 ± 22.78	85.33 ± 22.05	85.40 ± 21.74
Prevaccination oral temperature (°F)					
Mean ± SD	97.73 ± 0.70	97.77 ± 0.69	97.74 ± 0.70	97.76 ± 0.70	97.74 ± 0.70

Results of co-primary endpoints: immunogenicity analyses were conducted on the PP population, which minimally varied from the evaluable population, with less than 1% variation in the number of subjects in the two populations in either age cohort (18 to 64 years and ≥ 65 years age). The HAI antibody responses for QIV were shown to be

non-inferior for shared influenza A and B vaccine strains compared with TIV comparators for the co-primary endpoints of GMT and SCRs.

Post-vaccination GMTs, SCRs, and analysis of non-inferiority of QIV relative to TIV for each strain 21 days post-vaccination in adults (PP population)

Table 7. Post-vaccination GMTs, SCRs, and analysis of non-inferiority of QIV relative to TIV for each strain 21 days post-vaccination in adults (PP population)

Strain	Postvaccination GMT [a]		GMT Ratio [b]	Seroconversion rate (SCR) % [c]		SCR Difference [d]	Met both pre-defined non-inferiority criteria? [e]
	bioCSL QIV [f]	Pooled TIV (A strains) or TIV-1 (B/YAM) or TIV-2 (B/VIC)	Pooled TIV (A strains) or TIV-1 or TIV-2 over bioCSL QIV (95% CI)	bioCSL QIV [f]	Pooled TIV (A strains) or TIV-1 (B/YAM) or TIV-2 (B/VIC)	Pooled TIV (A strains) or TIV-1 or TIV-2 minus bioCSL QIV (95% CI)	
A/H1N1	303.0	280.2 [g]	0.92 [j] (0.87, **0.98**)	38.8	37.7 [g]	-1.1 [m] (-4.4, **2.2**)	Yes
A/H3N2	488.7	454.2 [g]	0.93 [j] (0.88, **0.98**)	40.9	39.3 [g]	-1.7 [m] (-5.0, **1.6**)	Yes
B/YAM	64.3	55.7 [h]	0.87 [k] (0.81, **0.93**)	31.0	27.8 [h]	-3.2 [n] (-7.0, **0.5**)	Yes
B/VIC	87.9	82.2 [i]	0.94 [l] (0.86, **1.01**)	40.3	38.7 [i]	-1.6 [o] (-5.6, **2.4**)	Yes

Source: Post-Text Table 14.2.1.1 and 14.2.2.1 (Section 14.2).
Abbreviations: A/H1N1: A/California/7/2009 (H1N1) pdm09-like virus; A/H3N2 = A/Texas/50/2012 (H3N2)-like virus; B/YAM: B/Massachusetts/2/2012-like virus (B/Yamagata lineage); B/VIC: B/Brisbane/60/2008-like virus (B/Victoria lineage); CI: confidence interval; GMT: geometric mean titer.
[a] Adjusted Analysis GMT Model: Log-transformed Postvaccination HI Titer = Vaccine + Age Group [18-49, 50-64, 65-74, ≥ 75] + Sex + Vaccination History [y/n] + Log-transformed Prevaccination HI Titer + Site + Age Group*Vaccine. LS Means were back-transformed.
[b] GMT Ratio = bioCSL TIV/bioCSL QIV. bioCSL TIV-1 and bioCSL TIV-2 are pooled for analysis of the A strains. For B/Yamagata TIV=TIV-1, for B/Victoria TIV=TIV-2
[c] Seroconversion rate was defined as the percentage of subjects with either a prevaccination HI titer < 1:10 and a postvaccination HI titer ≥ 1:40 or a prevaccination HI titer ≥ 1:10 and a 4-fold increase in postvaccination HI titer.
[d] Seroconversion rate difference = bioCSL TIV SCR percentage minus bioCSL QIV SCR percentage
[e] Non-inferiority (NI) criteria for the GMT ratio: upper bound of two-sided 95% CI on the ratio of Pooled TIV or TIV-1 (B/Yamagata) or TIV-2 (B/Victoria)/bioCSL QIV. GMT should not exceed 1.5. NI criteria for the SCR difference: upper bound of two-sided 95% CI on the difference between SCR Pooled TIV or TIV-1 (B/Yamagata) or TIV-2 (B/Victoria) – bioCSL QIV should not exceed 10%.
[f] bioCSL QIV, N=1691
[g] Pooled TIV (A strains), N=1704
[h] TIV-1 (B Yamagata), n=854
[i] TIV-2 (B Victoria), n=850
[j] Ratio of pooled TIV/bioCSL QIV
[k] Ratio of TIV-1 (B Yamagata)/ bioCSL QIV
[l] Ratio of TIV-2 (B Victoria)/ bioCSL QIV
[m] Pooled TIV - bioCSL QIV
[n] TIV-1 (B Yamagata) - bioCSL QIV
[o] TIV-2 (B Victoria) - bioCSL QIV

Results of secondary endpoints: For the secondary endpoints, the HAI responses were shown in the overall study population to be superior for QIV to the results for the alternate B strains for the TIV comparators for the same endpoints. Non-inferiority and/or superiority were also met for each of the serological endpoints of GMT and SCR separately in the two age cohorts (18 to 64 years and ≥ 65 years). Additional descriptive secondary endpoints including the percentage of subjects with a HAI titre ≥ 40 (SPRs), SCRs and GMFIs by study vaccine and age cohort were analysed. In general for these endpoints, results were similar between different study vaccines within each age cohort for A strain results, and when the vaccine included B strains were matched.

There were high rates of vaccination with influenza vaccine in the previous 12 months in the overall study population (Full analysis set (FAS): 63.3%) and in both age cohorts, but this was especially high in the older age cohort ≥ 65 years (81.6% versus 45.0% (18 to 64 years)). The post-vaccination SPRs for the A strains were very high (≥ 95%) and generally similar in both age cohorts. However, the post-vaccination SPRs for subjects ≥ 65 years of age were lower than the 18 to 64 years age cohort for the B strains, even when the B strains were matched. For example, for the B/Yamagata strain, the post- vaccination SPRs for QIV in adults aged ≥ 65 years was 57.5% and 84.3% in adults aged 18-64 years. For the B/Victoria lineage, the SPRs in adults aged ≥ 65 years was 68.3% and 86.7% in adults aged 18-64 years.

The SCRs in the overall study population (≥ 18 years) were generally in the range of 30 to 40% for both A strains and vaccine matched B strains. However, SCRs for subjects in the cohort ≥ 65 years of age were lower than the 18 to 64 years age cohort for all strains, even when the B strains were matched. For example, for the B/Yamagata strain, the SCR for QIV in older adults (≥ 65 years) was 16.6%, and 45.7% in adults aged 18 through 64 years. For the B/Victoria lineage, the SCR in adults aged ≥ 65 years was 23.5% and 57.6% in adults aged 18 through 64 years. A similar pattern to the B strain results were also seen for the two A strains for SCRs. Differences in age cohorts were also observed for GMFI. In general, relatively high SPRs and lower SCRs are a pattern that may be expected in study populations with high rates of influenza vaccination in the previous 12 months, as is the case in the US where the study was conducted.

The immunogenicity primary and secondary endpoints were met regardless of a subject's gender. Female subjects had slightly higher GMTs (both pre- and post-vaccination) for each strain versus males. Most subjects enrolled were White and not Hispanic/Latino. For these groups, the non-inferiority criterion for GMT and SCR and superiority of the alternate B strains for GMT and SCR were met for each strain and results were similar to the overall population. Post-vaccination (Day 21) GMTs and SCRs were generally higher for the black or African American race subgroup vs. the white subgroup, and for the Hispanic or Latino ethnicity subgroup compared to Not Hispanic or Latino subgroup.

In summary, HAI antibody responses for this QIV were shown to be non-inferior for matched influenza A and B vaccine strains versus TIV comparators in adults ≥ 18 years, for the co-primary endpoints of GMT and SCRs. Additionally, superiority for this QIV was shown for the same serological endpoints for the alternate (non-included) influenza B strains for the TIV comparators. These endpoints were also met for each of the two age cohorts separately.

Immunogenicity analysis against CHMP criteria: In relation to the evaluation of seasonal influenza vaccines, the CHMP criteria for the effective immunogenicity response defined in CPMP/BWP/214/96 are based on HI assay. The three immunogenicity endpoints and the criteria defined in the CPMP/BWP/214/96 guideline are as follows:

Table 8. Requirements for CHMP Criteria for Assessment of serological data

Serological assessment	Assessment criteria [a] for subjects aged between 18 and 60 years	Assessment criteria [a] for subjects aged over 60 years
The proportion of subjects achieving seroconversion or significant increase in antibody titre [b]	>40%	>30%
Geometric Mean Fold Increase (GMFI) [c]	>2.5	>2.0
The proportion of subjects achieving an HI titre ≥40	>70%	>60%

[a] As per the guidance, to meet the CHMP criteria, at least one of the assessments should meet the indicated requirements for each strain for the two age strata.

[b] Seroconversion was defined as achieving a post vaccination titre of ≥40 for those participants with a pre vaccination HI titre of <10; significant increase was defined as a four fold or greater increase in HI titre for those participants with a pre vaccination HI titre of ≥10.

[c] GMFI was defined as the geometric mean of the fold increases of post vaccination antibody titre over the pre vaccination antibody titre.

To meet the CHMP criteria, at least one of the three endpoints should meet the requirements for each strain included in the vaccine. The immunogenicity of this QIV was analysed according to the age cohorts (18 to < 60 years and ≥ 60 years). As shown in the table below: QIV met the target criteria for all strains in the adults 18 to < 60 years cohort, and both A strains and the B-Victoria strain for the older adults ≥ 60 years cohort. In the older adults ≥ 60 years cohort, for the B-Yamagata strain, the result for the Geometric Mean Fold Increase (GMFI) was precisely on the numerical target criterion of 2.0, but did not exceed 2.0 for that measure.

Table 9. Summary of the immunogenicity data for QIV (PP population) by age Cohort defined in CHMP Criteria

	Adult ≥ 18 to < 60 yrs N=740	Older Adult ≥ 60 yrs N=951
A/ (H1N1)		
Seroconversion Rate [a], n (%)	387 (52.3%)	269 (28.3%)
Geometric Mean Fold Increase (GMFI) [b]	5.7	2.5
Seroprotection Rate (HI titre ≥ 40), n (%)	735 (99.3%)	902 (94.8%)
OVERALL	PASS	PASS
A/ H3N2		
Seroconversion Rate, n (%)	425 (57.4%)	267 (28.1%)
Geometric Mean Fold Increase (GMFI)	5.7	2.5
Seroprotection Rate (HI titre ≥ 40), n (%)	733 (99.1%)	948 (99.7%)
OVERALL	**PASS**	**PASS**
B/Yamagata		
Seroconversion Rate, n (%)	354 (47.8%)	170 (17.9%)
Geometric Mean Fold Increase (GMFI)	4.3	2.0
Seroprotection Rate (HI titre ≥ 40), n (%)	644 (87.0%)	552 (58.0%)
OVERALL	**PASS**	[c]
B-Victoria		
Seroconversion Rate, n (%)	439 (59.3%)	243 (25.6%)
Geometric Mean Fold Increase (GMFI)	5.7	2.3
Seroprotection Rate (HI titre ≥ 40), n (%)	657 (88.8%)	652 (68.6%)
OVERALL	**PASS**	**PASS**

[a] Seroconversion rate was defined as the percentage of subjects with either a prevaccination HI titre < 1:10 and a postvaccination HI titre ≥ 1:40 or a prevaccination HI titre ≥ 1:10 and a 4-fold increase in postvaccination HI titre
[b] GMFI is defined as the geometric mean of the fold increases of postvaccination antibody titre over the prevaccination antibody titre
[c] The result for the Geometric Mean Fold Increase (GMFI) for Older Adults ≥ 60 years met the numerical target criterion of 2.0, but did not exceed 2.0.

Study CSLCT-FLU-05-09: Lot-to-Lot consistency for Seqirus TIVs in adults

This is a Phase III randomised, double-blinded, placebo controlled study conducted in approximately 1250 (up to 1350) US healthy adults (18 to < 65 years old). Randomisation was in a 1:1:1:1:1 ratio to receive 1 of 3 lots of vaccine in multiple-dose vials, a single lot of vaccine in prefilled syringes, or placebo in multiple dose vials (250 subjects per group). Randomisation was stratified according to age: 18 to 49 years and 50 to 64 years of age. A minimum of 63 subjects in the age range 50 to 64 was required in each group. Vaccine was prepared and administered by an un-blinded administrator, not involved in subsequent assessments. The study was conducted in in 2006 to 2007 Northern Hemisphere influenza season.

Key inclusion criteria were healthy adults aged 18 to < 65 years.

The study treatments were Seqirus influenza vaccine for the 2006 Southern Hemisphere influenza season with thiomersal, or thiomersal-free, or placebo via IM injection.

Influenza virus vaccine: 30 µg HA/strain/mL, thiomersal containing vaccine: 30 µg HA/strain/mL, thiomersal-free.

Placebo: sterile phosphate buffered saline, thiomersal-containing 0.5 mL dose.

The 4 formulations of the Seqirus Influenza Vaccine contain 45 µg of influenza HA antigens. Both forms of vaccine contain the following Southern Hemisphere 2006 recommended strains of Influenza virus per 0.5 mL dose: 15 µg of A/New Caledonia/20/99 (IVR-116) (H1N1)-like strain; 15 µg of A/New York/55/2004 (NYMC X-157) (H3N2)-like strain; 15 µg of B/Malaysia/2506/2004-like strain.

The primary objective was to demonstrate that vaccination with Seqirus influenza virus vaccine produces an immune response sufficient to meet the CHMP criteria for young adults of 40% seroconversion and 70% seroprotection. The co-primary endpoints were:

- The proportion of subjects with a minimum post-vaccination titre of ≥ 1:40. The lower bound of the 95% CI was to exceed 70% for each strain.
- The proportion of subjects with an increase in HI antibody titre of at least 4-fold, with a minimum post-vaccination HI titre of 1:40. The lower bound of the 95% CI was to exceed 40% for each strain.

Secondary immunogenicity endpoints were to demonstrate lot-to-lot consistency by comparison of GMT to influenza HA antigens after vaccination of the active treatment arms:

- Between the 3 lots of Afluria multi-dose vials and between Afluria multi-dose vials and the pre-filled syringe presentation.
- Lot-to-lot consistency was defined as meeting criteria that the lower and upper bounds of the 95% CI's for the GMT ratio between vaccine lots fall within the bounds of 0.667 to 1.5.

Immunogenicity analyses were carried out on the evaluable population. Descriptive statistics used to present all safety and immunogenicity results: n, mean, SD, median, maximum, and minimum for continuous data and frequency and percentage for categorical data. 95% CI were presented for some immunogenicity criteria. Geometric means and 95% CIs presented for the log-transformed immunogenicity parameters. Exact CIs based upon the binomial distribution were calculated for percentages. All analyses were performed with a significance level of 5% for 2–sided tests and 2.5% for one-sided tests.

A total of 1359 randomised of whom 823 received the thiomersal-containing vaccine; 266 received the thiomersal-free vaccine; and 270 received placebo. Populations analysed were: 1359 subjects; safety population n = 1357; evaluable population n = 1341; and PP population, n = 1241.

Immunogenicity results: with respect to the co-primary endpoints, overall (Seqirus influenza vaccine groups combined), a total of 48.7% (95% CI 0.456, 0.517) of subjects showed seroconversion for the A/New Caledonia strain; 71.5% (95% CI 0.687, 0.742) for the A/New York strain and 69.7% (95% CI 0.669, 0.725) for the B/Malaysia strain. Overall, 97.8% (95% CI 0.967, 0.986) of subjects who received Seqirus influenza vaccine met the post-vaccination criteria of seroprotection (titre ≥ 1:40) for the A/New Caledonia strain; 99.9% (95% CI 0.995, 1.000) of subjects for the A/New York strain and 94.2% (95% CI 0.927, 0.956) of subjects for the B/Malaysia strain. Following the logistic regression analysis of the co-primary endpoints, consistency was seen between Lots 1, 2 and 3 of the Seqirus influenza vaccine, multiple dose vial (thiomersal-containing) presentation with respect to post-vaccination HAI titres. Consistency was also shown between the Seqirus influenza vaccine multiple-dose vial (thiomersal-containing) presentation and the Seqirus influenza vaccine pre-filled syringe (thiomersal-free) presentation (GMT ratio fall within 0.667 to 1.5). Comparable GMT ratios between lots implied that the four vaccine treatment groups and the two different presentations used in the pivotal study elicited similar immune responses.

Table 10. Post-vaccination GMT ratios, lot-to-lot consistency (evaluable population)

Strain	Comparison	Ratio	95% CI
H1N1	CSL lot 1/2	1.092	(0.933, 1.278)
	CSL lot 1/3	1.017	(0.868, 1.191)
	CSL lot 2/3	0.931	(0.795, 1.090)
	CSL pf syringe/CSL md vial	1.020	(0.895, 1.164)
H3N2	CSL lot 1/2	0.839	(0.700, 1.005)
	CSL lot 1/3	0.929	(0.775, 1.114)
	CSL lot 2/3	1.107	(0.924, 1.327)
	CSL pf syringe/CSL md vial	1.039	(0.897, 1.203)
B Strain	CSL lot 1/2	1.167	(0.966, 1.410)
	CSL lot 1/3	1.058	(0.875, 1.280)
	CSL lot 2/3	0.907	(0.750, 1.096)
	CSL pf syringe/CSL md vial	1.065	(0.911, 1.243)

With regard to safety, the majority of subjects did not experience a systemic reaction or local reaction following vaccination on Day 0 and Day 4. Of those subjects who did, the reactions were mostly mild to moderate intensity.

Study CSLCT-USF-06-28: Efficacy study in adults for Seqirus TIV

This is a Phase IV, randomised, observer-blind, multi-centre, placebo-controlled study. Study vaccine was administered at Visit 1 (Day 0) and participants returned to the study site 21 days afterwards for an Exit Visit (Visit 2). Blood samples were collected at Visits 1 and 2 for immunogenicity assessments. During the 2008 season, blood samples were collected from all participants at Visit 1 and 2 and immunogenicity analysis was conducted on a randomly selected subset (n = 450). In 2009, blood samples were collected from only 450 participants at Visit 1 and 2. The study locations include multicentre in Australia and New Zealand. The study was conducted between February 2008 and January 2010. The key inclusion criteria were healthy adults 18 to < 65 years of age.

The study vaccine was a single vaccine; either 0.5 mL IM of Seqirus influenza vaccine: 30 µg HA/strain/mL, thiomersal-free; or placebo: sterile phosphate buffered saline, thiomersal-free.

Influenza HA antigens were: 2008 Season, A/Solomon Islands/3/2006 (H1N1)-like virus; A/Brisbane/10/2007 (H3N2)-like virus; B/Florida/4/2006-like virus.

2009 Season A/Brisbane/59/2007 (H1N1)-like virus; A/Brisbane/10/2007 (H3N2)-like virus; and B/Florida/4/2006-like virus.

The primary objective was to demonstrate that the efficacy of Seqirus influenza vaccine versus placebo in the prevention of laboratory-confirmed influenza A/B was significantly ≥ 40% in healthy adults. Secondary objectives were to demonstrate the efficacy of this IVV in prevention of lab-confirmed influenza A/B (due to strains matched to vaccine strains) was significantly greater than that of placebo in healthy adults. The secondary objective also includes the assessment of the safety and tolerability.

The primary efficacy endpoint is the incidence of laboratory-confirmed (culture/real-time reverse transcription polymerase chain reaction (RT-PCR)) influenza A/B infection with illness onset on or after Day 14. Secondary efficacy endpoints include:

- Incidence of laboratory-confirmed influenza A/B infection, by strains matched to vaccine strains, with illness onset on or after Day 14; this efficacy endpoint was included to control for any unanticipated mismatch between the virus strains circulating during the study period and those included in the study vaccine
- Incidence of influenza-like illness (ILI);
- Incidence of culture-confirmed ILI;
- Incidence of laboratory-confirmed ILI meeting the CDC ILI definition;
- Immunogenicity of influenza vaccine in a subset of study participants (SCR, SPR, GMFI).

Safety endpoints include the frequency and severity of solicited local and general AEs for 5 days, unsolicited AEs for 21 days, serious adverse event (SAEs) and new onset of chronic illness (NOCI) for 6 months after vaccination.

A randomisation scheme (2 vaccine: 1 placebo) was used to ensure the balance between treatments maintained. A total of 15, 044 were randomised, of whom 10,033 received the influenza vaccine (thiomersal-free) and 5,011 received placebo.

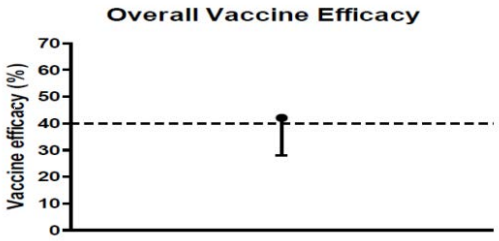
Table 11. Analysis populations for CSLCT-USF-06-28

Analysis Populations	2008 Season		2009 Season		Seasons Combined		Total
	Placebo	CSL's IVV	Placebo	CSL's IVV	Placebo	CSL's IVV	
Safety Population	2510	5030	2495	4985	5005	10,015	15,020
Evaluable Population for the:							
Clinical Endpoint Analysis	2501	5014	2459	4875	4960	9889	14,849
Immunogenicity Analysis	147	303	149	291	296	594	890

Note: The numbers of participants in the Per-Protocol Populations for both analyses were the same as the relevant Evaluable Populations.

Primary analysis of vaccine efficacy: during both the 2008 and 2009 influenza seasons, overall incidence of laboratory-confirmed influenza infection (due to any influenza A or B virus isolate) was lower in participants who had received Seqirus influenza vaccine (2.24%) than in those receiving placebo (3.87%). Overall efficacy for the prevention of laboratory-confirmed infection due to any influenza A or B virus during the 2008 and 2009 seasons was 42%, with a lower bound of the CI of 28%. The influenza vaccine was efficacious versus placebo (the lower bound of the CI exceeded zero), but the results did not satisfy the pre-defined criterion for success (that is, lower bound of CI being at least 40%). Thus the primary objective was not met.

Figure 2. Overall vaccine efficacy (%) with 95% CIs

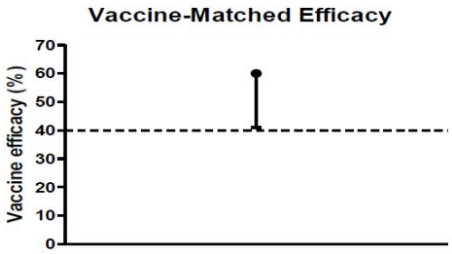


The assessment of vaccine efficacy in this study was complicated by the circulation of mismatched influenza virus strains in both the 2008 and 2009 Southern Hemisphere influenza seasons. In this study, > 60% of laboratory-confirmed influenza infections were caused by virus strains that were not included in the seasonal vaccines. In 2008, A/H1N1 and B strains that were not matched to vaccine strains accounted for 37% of WHO Collaborating Centre isolates; in 2009, the pandemic A/H1N1 strain accounted for approximately 73% of WHO Collaborating Centre isolates. Despite the unanticipated mismatch between circulating influenza strains and vaccine strains in 2008 and 2009, this study confirmed that this Seqirus influenza vaccine had clinical efficacy against infection caused by the vaccine influenza strains in both seasons.

Secondary analysis of vaccine efficacy for matched strains: the primary endpoint for most influenza vaccine clinical trials is typically defined in relation to vaccine-matched strains, not any influenza strain. In order to control for any unanticipated mismatch between the virus strains circulating during the study period and those included in the study vaccine, the secondary efficacy analysis was based on the vaccine efficacy over the 2008 and 2009 seasons combined for the prevention of laboratory-confirmed infection due to influenza strains matched to vaccine strains (vaccine-matched efficacy). The incidence of laboratory-confirmed infection due to vaccine-matched strains was low during the study period. Of the 192 participants in the placebo group who had a laboratory-confirmed influenza infection during the 2-year study period, only 73 participants had infections that were due to an influenza strain that was considered matched to one of the strains present in the vaccine for that particular season. During both the 2008 and 2009 seasons, the overall incidence of laboratory-confirmed influenza infection due to vaccine-matched strains was lower in participants who had received Seqirus influenza vaccine (0.59%) than in participants who had received placebo (1.47%). The efficacy of Seqirus influenza

vaccine for the prevention of laboratory-confirmed infection due to vaccine-matched strains during both seasons was 60%, with a lower bound of the CI of 41%. As the lower bound of the CI for vaccine matched efficacy exceeded 40%, the secondary vaccine efficacy objective was achieved.

Figure 3. Vaccine matched efficacy (%) with 95% CIs



Immunogenicity analysis: the robust antibody responses were elicited against all the vaccine strains and these have been discussed in detail in the CER (Attachment 2).

Safety analysis: The safety analyses of this study are discussed in Attachment 2. The safety endpoints include frequency and severity of solicited local and general AEs for 5 days, unsolicited AEs for 21 days, SAEs and NOCIs for 6 months after vaccination. The clinical evaluation concludes that there are no safety concerns identified in the study.

Clinical safety

The submitted clinical safety data have been assessed and summarised in the clinical evaluation report (see Attachment 2) and is repeated briefly in this overview. There is one pivotal study (Study CSLCT-QIV-13-01) which provided evaluable safety data for the QIV. The other two supporting studies do not utilise the QIV. The primary safety objective of Study CSLCT-QIV-13-01 was to assess safety and tolerability of QIV by the frequency and severity of: solicited local and systemic AEs for 7 days following vaccination (Day 1 to Day 7); cellulitis-like reaction, cellulitis and Grade 3 injection site induration/swelling for 28 days following vaccination; Unsolicited AEs for 28 days following vaccination; and SAEs for 6 months following vaccination.

The safety population is all subjects in the FAS who receive at least 1 dose of investigational product and have provided follow-up safety data. The analysis will be according to vaccination(s) received. A total of 1721/1741 QIV recipients included in the safety analysis.

All adverse events (irrespective of relationship to study treatment) in study CSLCT-QIV-13-01

No Adverse Events of Special Interest (AESIs), cellulitis or cellulitis-like reactions at the injection site or AEs leading to withdrawal were reported. Overall, 52.9% reported an AE (solicited local adverse reactions (36.5%), solicited systemic AEs (28.4%) and unsolicited AEs (20.8%)). These AEs were experienced in similar proportions of subjects across all the three vaccine groups.

Treatment-related adverse events (adverse drug reactions)

Most common (≥ 10% of subjects) solicited local adverse reaction was injection site pain in all three vaccine groups. The proportion in the QIV group experiencing injection site pain was higher in the 18 to 64 years age cohort (47.9%) versus the older age cohort (≥ 65 years: 24.6%). Additionally, the proportion of 18 to 64 year olds experiencing moderate redness and swelling/lump at the injection site was slightly higher in the QIV group (0.8% and 1.2%, respectively) versus TIV-1 (0.2% and 0.5% reported redness or

swelling/lump, respectively) and TIV-2 groups (0.5% of subjects reporting redness or swelling/lump each). Subjects aged ≥ 65 years also experienced redness and swelling/lump events of greater intensity (moderate (Grade 2) and severe (Grade 3)) in the QIV group versus comparator TIV vaccines. Female subjects in the QIV group were more likely to report any local adverse reaction (1.16 (95% CI: 1.01, 1.32)) and pain (at the injection site) (1.17 (95% CI: 1.02, 1.34)) than females in the TIV-1 group. Most of the solicited local adverse reactions (pain, redness and swelling/lump), experienced in any vaccine group, started on Day 1 and had a mean duration of 1.8 to 3.1 days.

The two most common (≥ 10% of subjects) solicited systemic AEs were myalgia and headache (in all 3 vaccine groups), in the adult cohort (18 to 64 years) and myalgia (followed by headache, but < 10% of subjects) in the older adult cohort (≥ 65 years). The proportion of subjects reporting any solicited systemic AE tended to be higher in the adult cohort (37.2% subjects overall) compared with the older adult cohort (19.6% subjects overall) regardless of the vaccine administered. Subjects were more likely to experience headache events after vaccination with QIV compared with TIV-1 for all subjects (1.35 (95% CI: 1.08, 1.68)), for subjects in the 18 to 64 years cohort (1.43 (95% CI: 1.10, 1.85)), for subjects in the 18 to 49 years age group (1.40 (95% CI: 1.02, 1.92)) and in females (1.42 (95% CI: 1.10, 1.83)). There were no statistically significant relative risks for any other systemic AEs after vaccination with QIV compared to TIV-1 and TIV-2. The average onset of solicited systemic AEs was on Day 2, with the exception of myalgia in all vaccine groups (average onset was Day 1), fever in the comparator TIV groups (average onset was Day 3) and vomiting in all vaccine groups (average onset was Day 3), and had a mean of 1.1 to 2.2 days.

Generally, the solicited local adverse reactions and systemic AEs were graded as mild in intensity. No individual unsolicited AE was reported in > 10% subjects in any vaccine group or age cohort.

The most common unsolicited AE was headache in 3.5% subjects overall followed by oropharyngeal pain (1.8%), back pain (1.7%), diarrhoea (1.2%), rhinorrhoea (1.2%), cough (1.0%) and nasal congestion (1.0%). The proportion of subjects experiencing any unsolicited AE was similar in the 18 to 64 years age cohort (20.5% subjects overall) compared with ≥ 65 years age cohort (21.2% subjects overall), with slightly higher proportion of subjects experiencing related unsolicited AEs in the 18 through 64 years age cohort (3.7% subjects overall) compared with ≥ 65 years age cohort (2.1% of subjects overall).

A higher proportion of female subjects reported events (solicited local or systemic and unsolicited AEs) versus male subjects in all vaccine groups. No clinically significant differences were noted in the proportion of subjects who reported events (solicited local or systemic or unsolicited AEs) based on race or ethnicity in any vaccine group. Grade 3 injection site swelling/induration was reported in more subjects in the QIV and in the ≥ 65 years age cohort (4 QIV subjects) compared with 18 to 64 years age cohort (one subject each in QIV and TIV-2 groups).

Deaths and other serious adverse events (SAEs)

A total of 89 SAEs were experienced in 66 subjects (1.9%) during the study, with 4 SAEs (asthma, pancreatitis acute, hypoxia and pneumonia experienced in 3 subjects in QIV group) assessed as related to study vaccine. A total of 2.3% subjects in the QIV group experienced one or more SAE versus 1.6% and 1.5% in the comparator TIV-1 and TIV-2 groups, respectively. During the active study period (Day 1 to Day 28), a total of 15 SAEs were experienced in 12 subjects.

There were 6 deaths reported during the study, one of which was assessed as related (pneumonia in the ≥ 65 years age cohort) to study vaccine. The SAEs with an outcome of death were: road traffic accident, cardiac failure, acute myocardial infarction, pneumonia

and ventricular arrhythmia (QIV group) and sepsis (TIV-2 group). Of these 6 subjects, 2 subjects died (road traffic accident and pneumonia) during the active study period (Day 1 to Day 28). The study was temporarily halted on two occasions (after serious, unexpected and related events of severe acute pancreatitis (occurred on Day 5) and severe asthma (occurred on Day 17; outside the 7 day halting rule period)). The Data and Safety Monitoring Board (DSMB) Chair was consulted and upon review of each event, recruitment was allowed to continue within 24 hours. A formal DSMB meeting was not required for either event.

No safety studies in special populations, such as in immunocompromised subjects, pregnant and breast feeding women, are available. There was one occurrence of pregnancy during Study CSLCT- QIV-13-01: one subject had a positive urine pregnancy test at Day 21 visit and 12 days later underwent an elective termination of pregnancy.

Clinical evaluator's recommendation

The clinical evaluator recommended authorisation of Afluria Quad.

Risk management plan

RMP Version 1.0 (dated 25 September 2015, data lock point 15 August 2015) and ASA Version 1.0 (dated 6 November 2015) were evaluated. The RMP evaluator recommended a number of revisions to the PI in the first round evaluation. The sponsor accepted many of the recommendations, however, disagreed with the recommendation to include a boxed warning stating that this vaccine can only be used in patients over 18 years of age (similar to the warning in the Fluvax TIV PI).

It was noted that in the sponsor's response to TGA questions, the sponsor committed that an updated RMP and ASA will be submitted to the TGA after the conclusion of evaluation.

The advice from ACSOV (Advisory Committee on the Safety of Vaccines) was sought for this submission. The ACSOV minutes were provided for advisory committee consideration.

Risk-benefit analysis

Delegate's considerations

Quality concerns

As detailed above (see Section II (Quality)) during initial evaluation, the quality evaluator identified several unresolved quality issues that may potentially impact the safety and efficacy of this vaccine.

Immunogenicity and safety data

The submitted pivotal study demonstrated the acceptable immunogenicity of the QIV in adults aged ≥ 18 years, based on the non-inferiority of the 8 co-primary immunogenicity endpoints for the 4 strains included in the QIV compared to two TIV comparators, and superiority for the QIV B strains not included in each of the two TIV comparators. Non-inferiority and superiority were also met for GMT and SCR in the two age cohorts (18 to 64 years and ≥ 65 years). There are no clinical efficacy data for the QIV, and the immunogenicity data are used as a surrogate for clinical efficacy. The efficacy of Seqirus TIV is supported by data from a large clinical study examining the efficacy of Seqirus TIV against laboratory-confirmed influenza in adults.

The safety profile of the QIV in the pivotal study is generally similar to that observed for the TIV-1 and TIV-2 vaccines. Solicited local and systemic reactions were more frequent in

adults 18 to 64 years of age compared to adults aged ≥ 65 years. Overall, the QIV is considered as having a clinically acceptable safety and tolerability profile in adults (≥ 18 years) at least in the number of patients included (n = 1721) in the pivotal study exposed to single dose QIV and included in the safety analysis. The safety of the Seqirus TIV in adults is supported by post-marketing surveillance data.

The clinical evaluator identified that there is a paucity of data in subjects of Asian ethnicity and Australian indigenous ethnicity, and there is a relative paucity of subjects in the younger age group (18 to 30 years). As the reactogenicity profile appears slightly worse in the younger age group overall, it will be important to gather further specific information on local and solicited vaccine-related AEs in the much younger age group if the QIV receives authorisation. There are no data on the immunogenicity and safety profile in immunocompromised patients and there is limited on the use of the QIV in pregnant women. These data should be collected during the post-marketing period.

The Delegate agreed that the submitted Study CSLCT-QIV-13-01 in adults has shown that the QIV is immunogenic and has a similar safety profile to Seqirus TIVs in the subjects included in this pivotal study.

Trade name for the QIV

TGA considerations

The TGA Delegate communicated to Seqirus in February 2016 regarding the concern of Fluvax Quad as the trade name for the QIV. The reason is that 'Fluvax' is easily misunderstood as a generic term for all influenza vaccines, and this misunderstanding can contribute to prescribing or administration errors. Seqirus provided a written response to the TGA on 31 March 2016. In the response, Seqirus stated that a name change has the potential to result in increased prescribing and administration errors due to the confusion created by the introduction of a new brand from a manufacturer with much less prescriber awareness than Seqirus Pty Ltd. Seqirus believes that capitalising on the substantial awareness built around the name 'Fluvax', in combination with the additional risk management activities outlined in the response, represents the optimal approach to minimising the risk of administration errors for the proposed product.

ATAGI considerations

On 4 April 2016, the chair of the Australian Technical Advisory Group on Immunisation (ATAGI) sent a letter to the TGA, raising concern about the trade name of Fluvax Quad. ATAGI considers that 'Fluvax Quad' is too generic and thus creates an unacceptable risk of incorrect and/ or inadvertent administration and the associated safety implications. The ATAGI discussed this issue during its 59th meeting in February 2016. ATAGI felt that 'Fluvax Quad' is not an appropriate trade name as it could be seen as a generic name and could cause confusion and resulting safety concerns. There are a number of QIVs available, targeting different age groups. In ATAGI's view, 'Fluvax Quad' has the potential to be mistaken as a generic term for any quadrivalent influenza vaccine. ATAGI notes that trade name proposed for this vaccine in other countries is far less generic including 'Afluria' in the US and 'Enzira' in the United Kingdom. The Delegate agrees with the ATAGI view on this.

ACSOV considerations

The following are extracted from the minutes of the Advisory Committee on the Safety of Vaccines (ACSOV) meeting on 3 February 2016:

'The committee advised against the approval of the proposed name Fluvax Quad. Risk minimisation activities by public health bodies and the sponsor since 2010 have emphasised the message 'Fluvax is not to be used in children under five years of age'; these activities make no mention of the valency of the vaccine. The relevant message for Fluvax Quad [Afluria Quad] will be 'do not use in children at all' (that is, only for adults), which initially

will be less memorable than the Fluvax TIV message that has been in place for several seasons. This creates a real potential that Fluvax Quad [Afluria Quad] will be used unintentionally off-label in children aged 5 to 18 years. This potential for use of Fluvax Quad[Afluria Quad] in children aged 5 to 18 years exists whether or not Fluvax TIV is supplied in the same influenza season and is present in the same refrigerator in a clinic.'

'The committee further commented that the trade name 'Fluvax' is effectively a contraction of 'influenza vaccine', which has/could lead to the name, 'Fluvax', being misunderstood as a generic term for 'influenza vaccine' and for 'Fluvax' to be seen as interchangeable with other influenza vaccines - this is not the case.'

'*The committee noted the size of the exposed populations for recently approved QIVs. For Fluarix Tetra, a total of 4,228 individuals were exposed to at least one dose of the vaccine in Phase III studies. For FluQuadri, clinical safety was addressed in three studies, involving 190 adults, 220 adults aged over 65 years of age, and 2339 children (6 months to 8 years of age). By comparison, there were only 1721 adult subjects in the population who received one dose of Fluvax Quad [Afluria Quad]. Further, the Fluvax Quad [Afluria Quad] trial was conducted in a single influenza season while trials for other QIVs were across more than one influenza season.'*

'In addition to a smaller total number of patients, the submitted RMP provided only limited information on safety data for Fluvax Quad [Afluria Quad] in special populations. Use in pregnant women has been identified as missing data, which is unfortunate given that pregnant women are considered to be more at risk of complications from influenza and are therefore targeted for vaccination via public health campaigns. Patients with comorbidities such as asthma were excluded from the clinical trial; this information is not stated in the PI.'

It is noted that at the December 2013 ACSOV meeting, the possible misuse of 'Fluvax' as a generic term was also discussed. The ACSOV members noted that it was easy to refer to all influenza vaccines as 'Fluvax' and suggested that the language used in all communications, including letters from the Chief Medical Officer, web statements and associated materials, could be modified in order to change this practice amongst vaccine providers. In particular, members suggested that all influenza vaccines be referred to by 'sponsor name, trade name', that is, 'Fluvax' should be referred to as 'bioCSL Fluvax', forcing a specificity in the terminology used. This could also be useful in the prevention of administrative errors, with members noting that the current Australian Childhood Immunisation Register (ACIR) reporting system listed 'Fluvax' as an option which providers can select. Members advised that if the option instead listed 'bioCSL Fluvax', providers will have to check the brand used and will be able to provide more specific, accurate reports.

The Delegate concurred with ATAGI and ACSOV with regards to the concern with the proposed trade name 'Fluvax Quad' for the reasons discussed in above. It should also be noted that the previous communication and education were targeting 'bioCSL's Fluvax'; and the relevant activities did not mention the valency of the vaccine. The sponsor has now changed its name from bioCSL to Seqirus. If this QIV is approved for use in adults in Australia, a different trade name is required to ensure safe use of the vaccine. Although there will be an initial requirement to educate health care professionals about a new name for a new QIV, the long term benefit is that Seqirus QIV will stand out for its own immunogenicity and safety features and will not be confused with any other influenza vaccines.

Summary of issues

- The quality evaluators have identified several unresolved quality issues which could potentially impact the safety and efficacy of this vaccine.

- One pivotal immunogenicity and safety study was submitted and the study demonstrated the non-inferiority (for the 8 co-primary endpoints) of the 4 strains included in the QIV compared to two trivalent influenza vaccines (TIVs), and superiority for the QIV B strains not included in each of the two TIVs. The safety profile of the QIV in this pivotal study is generally similar to that observed for Seqirus TIVs.
- No efficacy study is conducted for the QIV. An efficacy study for the sponsor's TIV was submitted.
- No lots to lots consistency study was conducted for the QIV. The lot-to-lot consistency data with the sponsor's TIVs were submitted.
- The proposed trade name, Fluvax Quad, is considered too generic and creates an unacceptable risk of incorrect and /or inadvertent administration and the associated safety implications.

Proposed action

The Delegate is not in a position to make a registration approval decision for Seqirus's QIV before the following issues are addressed to the satisfaction of the TGA:

- the unresolved quality issues identified by TGA quality evaluation
- an acceptable trade name
- any required revisions to the Product Information following the scheduled ACPM discussion
- submission of the updated RMP and ASA.

Request for ACPM advice

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

1. Could ACPM advice on the impact of the identified quality issues on the safety and efficacy of this QIV for the proposed use in adults?
2. Could ACPM advice on the acceptability of the proposed trade name Fluvax Quad?
3. RMP evaluator recommends: 'there should be a boxed warning stating that this vaccine can only be used in patients over 18 years of age, similar to the warning in the Fluvax TIV PI.' Seqirus disagrees with this and considers that the contraindication in children < 18 years (in the PI) is sufficient. Does ACPM consider a boxed warning is necessary?
4. Could ACPM advise on the acceptability of the lot-to-lot consistency data of Seqirus Pty Ltd's TIVs in supporting the lot-to-lot consistency of this QIV*?*

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 sponsor responded that the clinical data provided with the application supports the safety and efficacy of the sponsor's QIV for the indication sought in adults 18 years and above.

The sponsor also responded that the results from the pivotal QIV clinical in adults demonstrate that the sponsor's QIV is immunogenic and has a similar safety profile to the currently registered Fluvax TIV in adults. The sponsor's QIV is manufactured using the

same established process as Fluvax TIV for which there is a long standing demonstration of safety and efficacy in adults.

The sponsor agreed to change the proposed trade name to Afluria Quad, and provide the updated RMP and ASA.

The sponsor highlighted to TGA and the advisory committee that a significant body of work to further enhance product quality and characterisation has been conducted by the sponsor over the last few years. The sponsor reiterated its commitment to provide further information to address the quality questions to the TGA by September 2016.

On the basis of the information provided the sponsor stated their belief that all matters raised in the Delegate's Overview in relation to this application had been addressed.

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, agreed with the delegate and considered that it was not in a position to make a registration approval decision regarding Fluvax Quad [Afluria Quad] 0.5 mL pre-filled syringe containing a sterile, aqueous suspension for injection of quadrivalent seasonal influenza virus, unless the quality issues identified by TGA quality evaluation are resolved to the satisfaction of the Delegate of the TGA**.**

Proposed conditions of registration

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

Provision of a clinical lot-to-lot consistency studies conducted in adults or children as a post-marketing commitment.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Could the ACPM advice on the impact of the identified quality issues on the safety and efficacy of this QIV for the proposed use in adults?*

The ACPM noted that there were a number of unresolved issues in the quality evaluation with the most significant, control of impurities, having been linked to safety concerns. The ACPM advised that the quality issues raised could potentially be associated with adverse events following vaccination but were less likely to affect immunogenicity. The ACPM noted that the quality issues should be able to be addressed by the sponsor.

2. Could the ACPM advice on the acceptability of the proposed trade name Fluvax Quad *[Afluria Quad]*?

The ACPM noted that the sponsor in its pre-ACPM response agreed to change the proposed trade name to Afluria, which the ACPM noted was also the name of the TIV in the United States. The ACPM advised that Afluria Quad might be more appropriate, as it highlights the fact that the vaccine is quadrivalent which may minimise confusion.

3. *The RMP evaluator recommends: 'there should be a boxed warning stating that this vaccine can only be used in patients over 18 years of age, similar to the warning in the Fluvax TIV PI'. Seqirus disagrees with this and considers that the contraindication in children < 18 years (in the PI) is sufficient. Does ACPM consider a boxed warning is necessary?*

The ACPM advised that a boxed warning would be useful to highlight that the vaccine should only be given to adults.

4. Could the ACPM advice on the acceptability of the lot-to-lot consistency data of bioCSL's [*Seqirus Pty Ltd's]* TIVs in supporting the lot-to-lot consistency of this QIV?

The ACPM noted that no lot-to-lot consistency data had been presented for the QIV and that this was unacceptable. The ACPM advised that the sponsor should provide clinical lot-to-lot consistency studies conducted in adults or children as a post-marketing commitment, noting that the total HA content is increased from 45 (for TIV) to 60 (for QIV) µg per 0.5 mL dose.

Other advice

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.

The ACPM advised that pharmacovigilance activities are needed to ensure that patients under 18 years are not receiving this QIV.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Afluria Quad inactivated quadrivalent influenza vaccine (split virion), 60 µg HA/0.5 mL, suspension for injection, pre-filled syringe for intramuscular injection as in indicated for:

'the prevention of influenza caused by Influenza Virus, Types A and B contained in the vaccine. The vaccine is indicated for use only in persons aged 18 years and over.

See Precautions and Dosage and Administration.

For full details regarding recommendations for influenza vaccination, please refer to the relevant national immunisation guidelines.'

Initial specific conditions of registration applying to these goods

1. Condition to address outstanding quality issues including infectious disease safety
    a. Supply of Afluria Quad is not permitted until such time that Seqirus provides evidence to satisfy the TGA that:
        i. The manufacture of the product conforms to the EMA guidance EMA/CHMP/BWP/310834/2012 'Guideline on Influenza Vaccines - Quality Module' adopted by the TGA with an effective date of 1 November 2014.
        ii. For infectious disease safety aspects, the manufacture of the product either:

            a) conforms to the default standard European Pharmacopoeia General Monograph 01/2013:0153 (Vaccines for human use), which invokes 2.6.16 (Tests for extraneous agents in viral vaccines for human use; Chapter 2 Methods of Analysis); or

            b) has alternative measures applied that are effective at managing the infectious disease risks to an equivalent or greater level than the measures prescribed by the Methods of Analysis 2.6.16.

    The evidence requested above is required to be provided to the TGA by 15 September 2016. Any extension beyond this time frame would be subject to written agreement by the TGA.
2. Implementation of EU-RMP Version 2.0 (dated 23 June 2016, DLP 15 August 2015) with Australian Specific Annex Version 2.0 (dated 23 June 2016) revised to the satisfaction of the TGA and any future updates as a condition of registration.
3. Batch release testing by Laboratories Branch

- It is a condition of registration that all independent batches of Afluria Quad Vaccine intended for supply in the Australian market are not released until samples and the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

4. Certified Product Details

- An electronic copy of the Certified Product Details (CPD) should be provided upon registration of the therapeutic good. In addition, an updated CPD should be provided when any changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

Subsequent to the decision letter, the sponsor has provided sufficient evidence (in relation to Point 1 above) to satisfy the TGA that the product can be supplied.

Post-approval changes to the specific conditions of registration applying to these goods

Post-registration of Afluria Quad, a Quality (Category 3) application was submitted by the sponsor to TGA to satisfy condition 1 ' to address outstanding quality issues including infectious disease safety'. Following approval of the Category 3 application, TGA have varied the conditions of registration for Afluria Quad, removing condition 1.

Attachment 1. Product Information

The PI for Afluria Quad approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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