Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Influenza virus haemagglutinin

Proprietary Product Name: Afluria Quad

Sponsor: Seqirus Pty Ltd

November 2018

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.

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Common abbreviations

Abbreviation	Meaning
ACV	Advisory Committee on Vaccines
AE	Adverse event
AESI	Adverse event of special interest
ASA	Australian Specific Annex
CBER	Center for Biologics Evaluation and Research
CDC	Centers of Disease Control and Prevention
CHMP (CPMP)	Committee for Medicinal Products for Human Use
CI	Confidence interval
FAS	Full analysis sample
FDA	Food and Drug Administration
GBS	Guillain Barré syndrome
GCP	Good Clinical Practice
GMFIs	Geometric mean fold increases
GMR	Geometric mean ratio
GMTs	Geometric mean titres
gp	Group
HA	Haemagglutinin
HAI or HI	Haemagglutination inhibition
IB	Investigator Brochure
ICH	International Conference on Harmonisation
ILI	Influenza-like infection
IM	Intramuscular
ITT	Intention to treat
MEDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Meaning
mth(s)	Month(s)
NH	Northern Hemisphere
PI	Prescribing Information/Product Information
PP	Per protocol
PT	Preferred Term
QIV	Quadrivalent inactivated influenza vaccine
RMP	Risk Management Plan
SAE	Serious adverse event
SCR	Seroconversion rate
SCF	Seroconversion factor
SD	Standard deviation
SH	Southern Hemisphere
SOC	System Organ Class
SPR	Seroprotection rate
TDOC	Sodium taurodeoxycholate
TIV	Trivalent inactivated influenza vaccine
TRAE	Treatment-related adverse event
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WHO	World Health Organization
yrs	Years

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	1 February 2018
Date of entry onto ARTG:	2 February 2018
ARTG numbers:	262428, 294907
Active ingredient:	Influenza virus haemagglutinin
Product name:	Afluria Quad
Sponsor's name and address:	Seqirus Pty Ltd 63 Poplar Road Parkville VIC 3052
Dose form:	Suspension for injection
Container:	Pre-filled syringes each containing 0.5 mL
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 5 years and over.
Route of administration:	Intramuscular (IM)
Dosage:	The standard schedule for routine immunisation of persons over 5 years of age is one dose (0.5 mL). For previously unvaccinated children aged 5 to < 9 years, the recommended dosage is two doses at least four weeks apart.

Product background

This AusPAR describes the application by the sponsor (Seqirus Pty Ltd);[1] to extend the indications for inactivated quadrivalent influenza vaccine (Afluria Quad) to include paediatric use for the age of 5 years and above: It is currently approved for the prevention of influenza caused by influenza virus types A and B in adults 18 years and over. It is a quadrivalent influenza vaccine consisting of a clear, aqueous suspension packed in pre-filled syringes each containing 0.5 mL.

- Currently approved indication:

  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.

[1] Initial sponsor was CSL Ltd.

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

- Proposed indication for this application:

  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 5 years and over.

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

For the 2017 influenza season, each 0.5 mL dose contained 15 µg of influenza virus haemagglutinin from each of four types.

The standard schedule for routine immunisation of persons over 5 years of age is one dose (0.5 mL). For previously unvaccinated children aged 5 to < 9 years, the recommended dosage is two doses at least four weeks apart. Administration is by intramuscular (IM) or deep subcutaneous (SC) injection.

Regulatory status

At the time of this submission to TGA, applications to register Afluria Quad for use in persons 5 years and over had been submitted to the United States (US) (28 October 2016; approved by the US Food and Drug Administration (FDA) 31 August 2017), Canada (2 March 2017), Argentina (11 April 2017) and South Korea (28 July 2017). It had been previously approved in the US for:

§ *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*

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. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 1: Registration timeline

Description	Date
Submission dossier accepted and first round evaluation commenced	3 January 2017
First round evaluation completed	31 May 2017
Sponsor provides responses on questions raised in first round evaluation	29 June 2017
Second round evaluation completed	1 August 2017

Description	Date
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	5 September 2017
Sponsor's pre-Advisory Committee response	18 September 2017
Advisory Committee meeting	4 October 2017
Registration decision (Outcome)	1 February 2018
Completion of administrative activities and registration on ARTG	2 February 2018
Number of working days from submission dossier acceptance to registration decision*	200

* Legislative timeframe is 255 working days (see *Therapeutic Goods Regulations 1990*).

III. Quality findings

Introduction

The drug product is presented in 1 mL clear glass syringes with each syringe containing 0.5mL of vaccine with a nominal 60 µg haemagglutinin (HA) antigen, comprising a nominal amount of 15 µg of each of four subtypes of virus. The current presentation has a fixed needle attached to the syringe.

Evaluation summary and issues of importance

As this application sought an extension of the indication, relatively few data were provided in the submission that relate directly to the quality and safety of the drug product under the proposed change. The data provided by the sponsor for the submission was considered in conjunction with the existing data previously reviewed. The approach taken in the quality evaluation was to summarise the available quality data, as it relates to the proposed change; and to identify the potential risks to quality and safety of the product for the proposed indicated group.

The primary evaluation indicated no quality issues directly impacted by the proposed change.

However, the primary evaluation did identify a number of quality issues potentially impacting the safety of the product for the proposed change in indication from 18 years and above to 5 years and above. These issues and the associated concerns are listed below. Where the concerns have subsequently been addressed through the Section 31 process has been indicated.[2]

[2] The Section 31 process involves evaluation of the sponsor's responses to TGA questions and requests arising from the first round evaluation stage. The sponsor later addressed all relevant Section 31 requests. TGA was satisfied with the responses and the quality profile for the proposed change in indication.

Validated splitting conditions

During evaluation, the sponsor clearly indicated that all strains would, in future, be split with a minimum sodium taurodeoxycholate (TDOC) concentration. All of the relevant sections of the dossier were updated accordingly.

The changes were made to the dossier in response to questions raised in another evaluation. This issue has therefore been addressed and the wording for the TDOC splitting concentration should be taken as follows:

> *A set concentration of TDOC will be used for each new virus strain to be included in the vaccine. However, due to potential strain specific differences, a working range of TDOC will be maintained. Use of TDOC concentrations other than the set concentration will be justified in the Annual Strain Update variation.*

This issue has therefore been resolved. There are no issues arising.

Clinical trial needle length

The primary evaluation identified that while the currently registered drug product (and therefore the product to be used in the proposed indicated population) is presented in a pre-filled syringe with a fixed needle, that this presentation was not used for the clinical trials. Instead, the attention of the Delegate is drawn to the statements made regarding the needles used in Clinical Trials CSLT-QIV-13-01 and CSLT-QIV-13-02, that is:

- The vaccines were provided in a needle-free presentation
- The trial investigator determined the needle size and gauge 'appropriate to the person's age and body mass' (National Center for Immunization and Respiratory Diseases 2017).

There are no further quality issues arising from this issue.

Virally derived impurities

The primary evaluation identified that potential safety risks for the proposed indicated population may arise from failure to control the presence of virally derived impurities (in particular viral lipid) through the manufacturing process. Indeed, the sponsor has stated the following about the adverse events of 2010 associated with Fluvax:

> *The outcomes from the scientific investigations demonstrated that (a) an inverse relationship exists between the level of detergent used for splitting the influenza virus (TDOC) and the level of lipid but not RNA, present in the vaccine formulation, and (b) that the pyrogenic potential of MPH is dependent on the lipid levels as the lipid facilitates uptake/delivery of RNA.*

Therefore, a risk-associated factor in the sponsor's own opinion is the lipid content of the drug product. While lipid content per se is a risk-indicating factor, further corroboration of the potential risk profile of a given drug substance/product may also be extrapolated from the potential pyrogenic response estimated from the NF-κB Activation assay.

Given the events of 2010, the subsequent studies undertaken by the sponsor to identify contributing factors to those events and the outcomes of those studies, a model can be constructed for evaluating the potential risk of the product for the proposed indication. The model should show a clear link between a quantitated risk-associated parameter (lipid content), a known clinical outcome (the febrile events of 2010) and the test result for the surrogate of that clinical outcome (HEK-293 response in the NF-κB Activation assay). Co-titration of the test parameters (lipid content and HEK-293 assay) on material known to produce the known clinical outcome would then be able to indicate thresholds (limits) for these risk-associated parameter(s).

The sponsor did not demonstrate the above in the data provided through the current submission. Nevertheless, through the documents and commitments made in response to the Section 31 questions and the response to the second-round evaluation, the sponsor has proposed a control strategy that is considered acceptable.

Drug substance accepted on the basis of the control strategy is then used to formulate the drug product. The company are also proposing to test batches of the drug product with the NF-κB Activation assay with a titration based approach similar to that described above for the drug substances as an interim measure between now and the first intended supply date for the product into the proposed indicated population in Australia (early 2019 for the 2019 SH influenza season). [3]

Clearly the overall utility of the above strategy will only be evident after additional data are available. Hence, it is not possible to approve this strategy at the current time. Therefore, in the absence of the above data an approach must be found to allow release of the product until further data become available. The current Action Limits that have been applied for the current indication (18 years and over) cannot obviously be approved for the product in the proposed indicated population as it is not suitable for the 5 to 17 year old cohort. Therefore, clinical trial batches used in the indicated population provide the only baseline from which thresholds (limits) for risk-associated parameters can be derived.[4]

At the current time only a single batch of Afluria Quad has been used in the proposed indicated population namely, 0904-03401. This batch has been shown through the clinical trial to have an acceptable safety profile. The quality profile of this batch of vaccine can therefore be used to define the quality profile for future batches of vaccine intended for the target population. First, the vaccine has been shown to induce a negative response in the NF-κB Activation Assay. Second, the component MPHs used to manufacture the batch have all been tested for lipid and RNA content and have also been shown to be negative in the NF-κB Activation Assay.

The sponsor had also requested that the data from the clinical trials in those under 5 years of age also be considered and the Delegate has advised that these data have recently been reviewed and that they will consider these in the decision. On this basis, the quality data for the QIV batch from Clinical Trial CSLCT-QIV-15-03 (0904-03501 and 0904-03502) are also considered suitable for setting limits for the proposed indicated population.

The most precautionary approach at the current time to control of the drug product for the proposed indicated population i.e. persons 5-17 years-old, would therefore be to apply limits, based on the values of batches utilised in the Clinical Trials CSLT-QIV-13-01, CSLT-QIV-13-02 and CSLT-QIV-13-03, to each batch of product and to also test representative batches for pyrogenic potential through the NF-κB Activation Assay.

Summary

The sponsor has proposed a control strategy for release of the drug product into the proposed indicated population that appear to offer the potential to reduce the risk of clinical outcomes similar to those of 2010 occurring with the current vaccine. An assessment of the success of the strategy is dependent on the generation of additional quality data from the forthcoming 2018 SH and 2018/19 NH influenza seasons and subsequent approval of the strategy by TGA. In the interim it is suggested that a condition of registration be placed upon the product to restrict release to those batches that meet a specification for total lipid content (expressed in μg/ml for the formulated drug product)

[3] The Section 31 process involves evaluation of the sponsor's responses to TGA questions and requests arising from the first round evaluation stage. The sponsor later addressed all relevant Section 31 requests. TGA was satisfied with the responses and the quality profile for the proposed change in indication.
[4] The control strategy and action limits proposed was later considered acceptable and approved.

and that are based on content of vaccines shown to have an acceptable safety profile in the indicated population.

Recommendation

The quality evaluation for the proposed change of indication from 18 years and over to 5 years and over has identified control of the drug product for release into the market would best be achieved by establishing quality limits from material shown to have an acceptable safety profile and that are effective in the proposed indicated population. The sponsor has proposed a future strategy for the future release of the product that should not be approved at the current time until additional data as indicated by the sponsor is provided and evaluated in a separate submission. Consideration may be given to implementing specific conditions of registration to allow the sponsor to address these issues if the Delegate considers this appropriate.

Proposed conditions of registration

Batch release testing and compliance with the certified product details (CPD)

It is a condition of registration that:

- The first three batches of final bulk vaccine for each seasonal product be tested in the NF-kB activation assay, and that the assay be adapted to perform the testing under standard conditions and with at least one further dilution at a minimum 4 fold increase in concentration
- The lipid content for each strain be calculated (in mg/ml) for each batch of final bulk vaccine, and that limits be applied to each type/subtype based on the lipid content levels determined for clinical trial lots.

In addition to the above conditions of registration, it is also a condition of registration that all independent batches of Afluria Quad are not released for sale until samples and the manufacturer's release data have been assessed and you have received notification acknowledging release from the Laboratories Branch, TGA.

For each independent batch of the product supplied in Australia, the sponsor must supply the following:

- A completed Request for Release Form.
- Complete summary protocol for manufacture and quality control.
- At least 40 doses of each final batch of finished drug product with the Australian approved labels, PI and packaging.
- Any other samples, reagents, reference material and standards required to undertake testing, as requested by Laboratories Branch, TGA.

Distribution of each batch of vaccine is conditional upon fulfilment of these conditions and receipt of a letter from the Laboratories Branch acknowledging release.

Samples and data should be forwarded to the influenza Group, Immunobiology Section, Laboratories Branch [at the TGA] before release of each batch and with sufficient lead time to allow for Laboratories Branch testing.

IV. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

V. Clinical findings

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

Introduction

Clinical rationale

Influenza is a highly infectious disease that occurs in epidemics throughout the Northern Hemisphere (NH) and Southern Hemisphere (SH) winter months. Trivalent inactivated and live attenuated influenza vaccines have been the mainstay of influenza prevention. Each year in Australia, influenza infection affects approximately around 5 to 10% of the general population, up to 20% in some years. Among Australian patients aged ≥ 50 years, influenza is annually associated with > 3,000 deaths and > 13,500 hospitalisations. Two genetically distinct lineages of influenza B viruses have co-circulated since 1985.[5] On average, influenza B strain accounts for approximately 25% of positive specimens in the US.[6]

The burden of infection due to influenza B is largely school age children, young adults and the elderly; however, young children experience the highest mortality with 34% of reported paediatric influenza deaths in the US due to B strain infections.[7] Mismatches between the B strain in the vaccine and the circulating strain occur in approximately 5 out of every 10 influenza seasons.[8] The US Centers for Disease Control and Prevention (CDC) has estimated that in a season where there is a B strain mismatch, availability of QIVs could have reduced annual influenza cases (range: 2200 to 970,000), hospitalisation's (range: 14 to 8200), and deaths (range: 1 to 485) in the US.[9] These findings are similar in Australia whereby data collected from 2000 to 2011 revealed poor matches with the recommended vaccine virus and the circulating B-lineage virus in 4 of the 12 years reviewed, and partial matches in 3 out of 12 influenza seasons.[10]

The avoidance of this B strain mismatch has been one of the main drivers of the development of (and approval) of quadrivalent vaccines with representative strains of both major B strain lineages. While Afluria Quad is now approved for use in those aged 18 years and older, this application seeks to extend the indication to children aged 5 years or older, in order to minimise the effects of 'B' strain mismatch in the annual vaccine, and the morbidity and mortality costs associated with this mismatch when it does occur.

[5] Rota PA, Wallis TR, Harmon MW, Rota JS et al. Cocirculation of two distinct evolutionary lineages of influenza type B virus since 1983. Virology 1990 Mar; 175(1):59-68.
[6] Ambrose CS, Levin MJ. The rationale for quadrivalent influenza vaccines. Hum Vaccin Immunother 2012; 8(1):81-8.
[7] Belshe, RB. The need for quadrivalent vaccine against seasonal influenza. Vaccine 2010 Sep 7; 28 Suppl 4: D45-53.
[8] Belshe, RB. The need for quadrivalent vaccine against seasonal influenza. Vaccine 2010 Sep 7; 28 Suppl 4: D45-53.
[9] Reed C, Meltzer MI, Finelli L, Fiore A. Public health impact of including two lineages of influenza B in a quadrivalent seasonal influenza vaccine. Vaccine. 2012 Mar 2;30(11):1993-8.
[10] Barr IG, Jelley LL. The coming era of quadrivalent human influenza vaccines: who will benefit? Drugs. 2012 Dec 3;72(17):2177-85. Erratum in: Drugs. 2012 Dec 3;72(17):2186.

Guidance

At pre-submission meetings held with the TGA during 2016, the sponsor discussed that data from a supportive TIV safety study (Study CSLCT-USF-10-69) would be included in this application. Study CSLCT-USF-10-69 is a Phase IV safety and tolerability study, with the primary objective to evaluate the frequency and intensity of fever in children aged 5 to < 9 years in the 7 days after each administration of the NH 2014 to 2015 influenza season. This study was felt to be relevant and informative to the paediatric clinical development program for Afluria Quad, as during the SH 2010 season, there was an unexpected increase in severe fever and fever related events observed in the paediatric population, increased reports of fever events were also observed in children aged 5 to < 9 years. Following the conclusion of the scientific investigations into the 2010 adverse events, it was thought that modification of the splitting conditions of the B strain by increasing the concentration of the splitting agent TDOC may reduce the potential for pyrogenic vaccine responses. Therefore before initiating the Afluria Quad development program in persons aged less than 18 years, Study CSLCT-USF-10-69 was conducted to gather a contemporary fever rate in this age group, using the NH US licensed 2014 to 2015 Seqirus TIV formulation where the B strain was split with a higher concentration of TDOC.

As the Afluria Quad clinical development program for the adult and paediatric studies are closely related, the paediatric clinical information from Studies CSLCT-QIV-13-02 and CSLCT-USF-10-69 have been integrated into the previously submitted and approved clinical overview and summary modules. Subsections have been created within these modules to include information from Studies CSLCT-QIV-13-02 and CSLCT-USF-10-69 and existing headings amended to differentiate between the adult and paediatric sections, as required. Seqirus has also updated the section within the Clinical Overview regarding clinical lot-to-lot consistency rationale for Afluria Quad. This section now provides further explanation and clarity about demonstration of the lot-to-lot consistency for Afluria Quad, including demonstration of lot-to-lot consistency of the immune response from clinical Study CSLCT-QIV-13-01, as well a summary of the number of influenza vaccine lots assessed over several seasons and influenza virus strains in the QIV development program.

The sponsor also recently received approval from the TGA to amend the confidence interval (CI) interval results for Study CSLCT-QIV-13-01 (conducted in adults) listed in the Clinical Trials section of the approved Afluria Quad PI. This minor amendment was in response to a request by the US FDA during their recent evaluation of Afluria Quad to recalculate the non-inferiority post-vaccination geometric mean titre results and 95% CI using exact methods for the difference in seroconversion rates. Although these changes have no impact on the immunogenicity results of the Study CSLCT-QIV-13-01 or any change to the overall study conclusions, the sponsor has taken the opportunity to align the tables and figures with the TGA approved PI amendment for completeness.

Contents of the clinical dossier

The submission contained the following clinical information:

- Study CSLCT-QIV-13-02: A Phase III, randomised, multicentre, observer-blinded, non-inferiority study to evaluate the immunogenicity and safety of a bioCSL quadrivalent inactivated influenza virus vaccine (bioCSL QIV) with a US licensed 2015-2016 quadrivalent inactivated comparator influenza vaccine (comparator QIV) in a paediatric population 5 through 17 years of age;
- Study CSLCT-USF-10-69: A Phase IV, multicentre, randomised, observer-blind, parallel-arm study to evaluate the safety and tolerability of CSL's influenza virus vaccine in children 5 to less than 9 years of age;

- Validation (by Focus Diagnostics, Inc) of the haemagglutination inhibition (HAI) Test for Titrating Influenza A and B Specific Antibodies (TSOP.119.057); (CSL: 2015-2016 Vaccine Strains i.e. A/California/7/2009 (H1N1) A/South Australia/55/2014 (H3N2),B/Phuket/3073/2013, B/Brisbane/60/2008);
- Addendum to clinical study report for Study CSLCT-QIV-13-01 (a Phase III, randomised, multicentre, double-blinded study to evaluate the immunogenicity and safety of quadrivalent influenza vaccine (CSL QIV) in Comparison with a US licensed 2014 to 2015 trivalent influenza vaccine (CSL TIV-1), and a trivalent influenza vaccine containing the alternate B strain (CSL TIV-2), in adults aged 18 years and above. This report is not directly relevant to this application. This addendum is to report responses to requests dated 20 May 2016 by the US FDA CBER for information additional to that in the final Clinical Study Report (CSR) for Study CSLCT-QIV-13-01, dated 16 July 2015.

In summary:

- The non-inferiority post-vaccination geometric mean titre (GMT) analysis results of the CSR have been updated using the model specified in the Statistical Analysis Plan (SAP), namely:
  - Log-transformed post-vaccination HI titre = vaccine + age group (18 to 49, 50 to 64, 65 to 74, or ≥ 75) + sex + vaccination history (yes/no) + Log-transformed pre-vaccination HI titre + site. The model specification noted above excludes the non-significant age-by-vaccine interaction term.
- Exact 95% CIs for the difference in seroconversion rates (SCRs) have been recalculated using exact methods as specified in the SAP. In addition, the table footnote regarding the method of computing the CI for the difference in SCR has been revised to read: 'The exact 95% CI for the difference in seroconversion rates between CSL TIV and CSL QIV based upon the binomial distribution.' As a consequence of these recalculations, the SCR results have also been updated.
- The recalculated results have no discernible impact on the non-inferiority of bioCSL QIV versus bioCSL TIV in terms of geometric mean titre (adjusted GMT ratios) in adults aged ≥ 18 Years (per-protocol population) and non-inferiority of bioCSL QIV versus bioCSL TIV in terms of seroconversion rates (%) in adults aged ≥ 18 years for each strain (per-protocol population). There is no impact on any other immunogenicity results or any change to the overall conclusions of the study. These data will not be discussed further in this application as they are not of direct relevance.

Paediatric data

This application seeks to extend the indication for use of Afluria Quad to children aged 5 years or older.

Good clinical practice

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. The studies presented in this application were conducted in accordance with Good Clinical Practice (GCP).

Pharmacokinetics

With respect to the nature of the product, clinical pharmacology data have not been assessed. The split virion, inactivated influenza vaccine, as all vaccines, induces antibodies,

which consecutively are responsible for the desired effect of the intervention, that is, protection against an infectious disease. The constituents of the vaccine itself are phagocytosed at the site of injection. Therefore, specific interaction or pharmacokinetic studies have not been carried out in humans.

Dosage selection for the pivotal studies

The dose of Afluria Quad used in the pivotal paediatric study was the same as that approved for use in adults aged 18 years or older, that is, single dose of 0.5 mL IM. For previously unvaccinated children aged 5 to < 9 years, the recommended dosage is two doses at least four weeks apart.

Efficacy

Studies providing efficacy data

The pivotal paediatric Study CSLCT-QIV-13-02 not an 'efficacy' study, rather the derived immunogenicity data is used as a surrogate for clinical efficacy. This is a standard approach in influenza vaccine studies. The study was designed according to the Guideline on Clinical Evaluation of New Vaccines.[11] Anti-haemagglutinin (HA) antibody response is an established correlate of protection against influenza in adults and children; therefore, HI titre was the primary outcome measure in this study.

In accordance with the guidelines indicated by EMA:

- Any HI result < 10 (= undetectable);
- sera which have a titre ≥ 10 but < 40 are considered positive but not protective;
- sera with a titre ≥ 40 are considered positive and protective.

Studies providing evaluable efficacy data

The pivotal Study CSLCT-QIV-13-02 provides indirect evidence of 'efficacy' through serological responses to the vaccine which have been determined, over time, and from multiple sources, to have clinical efficacy either in protecting against influenza acquisition or attenuating the course of the infection if infection is not completely prevented through vaccination.

Evaluator's conclusions on efficacy

Study CSLCT-QIV-13-02 was conducted entirely within the US over one NH flu season (2015 to 2016), in children aged 5 to 17 years, the majority of subjects were of white ethnicity; 51% (n = 1166) in the FAS population were in the younger age group (aged 5 to 8 years). Standard methodology to demonstrate immunogenicity was utilised. The non-inferiority of Afluria Quad versus an approved QIV was demonstrated through the eight co-primary endpoints of HI GMT and SCR for each viral strain included in the vaccines. Secondary immunogenicity findings also supported the primary endpoint conclusions. There was no difference in vaccine 'efficacy' between the age strata. There were no safety concerns raised, the safety data is discussed in greater detail below.

[11] EMEA/CHMP/VWP/164653/2005: Guideline on Clinical Evaluation of New Vaccines

Safety

Studies providing safety data

Pivotal studies that assessed safety as the sole primary outcome:

- Study CSLCT-USF-10-69; this is not a pivotal study but a supporting safety study.

Pivotal and/or main efficacy studies:

- Study CSLCT-QIV-13-02; immunogenicity results described above.

Patient exposure

As this is an application seeking approval of Afluria Quad in children/adolescents aged 5 to 17 years of age, the safety data in adults is not of direct relevance. See below for a summary of the safety populations in Study CSLCT-QIV-13-02.

Table 2: Study CSLCT-QIV-13-02 Number and % of subjects in each analysis population

Analysis Populations	Seqirus QIV (n = 1709)	Comparator QIV (n= 569)	Total (N = 2278)
Full Analysis Set, n (%)	1709 (100)	569 (100)	2278 (100)
Overall Safety Population, n (%)	1692 (99.0)	560 (98.4)	2252 (98.9)
Solicited Safety Population, n (%)	1621 (94.9)	535 (94.0)	2156 (94.6)
Solicited Safety Population After 1st Vaccination, n (%)	1618 (94.7)	532 (93.5)	2150 (94.4)
Solicited Safety Population After 2nd Vaccination, n (%)	178 (10.4)	63 (11.1)	241 (10.6)

Source: Module 5, Section 5.3.5.1 CSLCT-QIV-13-02, Table 11.1-1, Post-Text Table 14.1.1.1.

Safety issues with the potential for major regulatory impact

Liver function, liver toxicity, renal function, renal toxicity, other clinical chemistry, haematology and haematological toxicity

Not assessed.

Electrocardiograph findings and cardiovascular safety

Not applicable, not assessed.

Vital signs and clinical examination findings

None revealed.

Immunogenicity and immunological events

None revealed.

Serious skin reactions

One subject who received the Seqirus QIV experienced a 'cellulitis-like reaction'. This subject experienced Grade 3 pain, Grade 3 swelling (up to 78 mm), and Grade 3 redness (up to 78 mm) concurrently from Day 3 to 7 after the first vaccination into right deltoid muscle. Investigator assessed and confirmed not cellulitis.

Post-marketing data

Not applicable.

Evaluator's conclusions on safety

Safety data was provided for Afluria Quad from a single study conducted during the NH 2015 to 2016 season, Study CSLCT-QIV-13-02. In this study, the Seqirus QIV contained the 4 influenza strains split with a higher concentration of TDOC. In total, 874 children aged 5 to 8 years and 834 children/adolescents aged 9-17 years received at least 1 dose of Afluria Quad. Fever rates were comparable to the QIV comparator, in both age groups. There was a slight excess of local injection site reactions (pain/swelling/redness) in the younger age group compared to the comparator QIV, although these resolved quickly. There was also a slight excess of severe solicited local adverse reactions in the Seqirus QIV recipients versus Comparator QIV. One Seqirus QIV patient (aged 8) had a 'cellulitis like reaction' with grade 3 pain/swelling/redness which lasted through to Day 7 post vaccination. In the older age group myalgia was 1.5 fold more likely to be experienced in the Seqirus QIV recipients. Although relatively small numbers of subjects received a second vaccine on study, there was no evidence that receipt on the second vaccine was associated with an excess of solicited local and systemic side-effects, or unsolicited adverse events; in general the second vaccine was better tolerated. Study CSLCT-USF-10-69, provided supportive safety data for Seqirus TIV (2014 to 2015 NH season product), in which the H3N2 and B strains were split at the upper levels of TDOC concentration. In total there were 292 children aged 5 to 8 years in the safety analysis set for 1st vaccination. When considering historical fever rates in previous paediatric clinical studies (Studies CSLCT-USF-07-36, CSLCT-USF-06-29 and CSLCT-FLU-04-05) in the same age group, overall and severe fever rates were lower in children vaccinated with the Seqirus TIV manufactured using higher TDOC splitting conditions for the H3N2 and B strains.

The clinical reviewer notes the reporting of an SAE ('severe delirium febrile') which was reported as 'expected' and then later reassessed as 'unlisted/unexpected'. This event was reported to the Data and Safety Monitoring Board chair. In summary, with respect to the safety data arising from Study CSLCT-QIV-13-02, Afluria Quad appears to have an acceptable safety profile in both age groups enrolled.

First round benefit-risk assessment

First round assessment of benefits

The first round assessment of benefits is given in Table 3, below.

Table 3: First round assessment of benefits

Indication	
Benefits	Strengths and Uncertainties
1. Afluria Quad in the proposed usage provides non-inferior 'coverage' (antibody seroconversion and other standard measures of immunogenicity) against all 4 influenza strains contained in the vaccine versus an approved US comparator QIV. 2. Safety profile of this QIV is similar to the comparator QIV. 3. Safety data from Study CSLCT-USF-10-69 is supportive, although it used a TIV	1. Data are robust, study design appropriate with adequate power, standard immunogenicity endpoints. 2. Safety data provided for only 874 in the younger age group (5 to 8 years), the evaluator feels uncertain with this new QIV and with all 4 split with the higher percentages of TDOC, that this is sufficient immunogenicity and

Indication	
vaccine, with 2 of the 3 strains split with the higher concentrations of TDOC.	safety data. 3. While the safety data from Study CSLCT-USF-10-69 study is reassuring, it did not use Afluria Quad, and is underpowered for the comparator arm. No immunogenicity data provided in this study. 4. Other QIV flu vaccines available, so this QIV will not fill a 'gap in the market'.

First round assessment of risks

The first round assessment of risks is given in Table 4, below.

Table 4: First round assessment of risks

Risks	Strengths and Uncertainties
1. No data on the immunogenicity and safety profile in immunocompromised patients as these subjects were specifically excluded from participation. 2. Data supplied is over one NH season, in one country, predominantly children of white ethnicity enrolled, only 874 younger children aged 5 to 8 years exposed, are these data representative for a new formulation of QIV? 3. Hardly any data for the QIV in subjects of Asian ethnicity, this is of direct relevance to Australia. 4. No data for the QIV in Australian indigenous ethnicity – this is of direct relevance to Australia.	1. Flagged in the PI; as detailed in the RMP. Other routine measures including monitoring and reporting of post-marketing safety data and signal detection in the immunocompromised.

First round assessment of benefit-risk balance

While the data arising from this single Study CSLCT-QIV-13-02, demonstrate that Afluria Quad appears safe and immunogenic against all 4 influenza strains (2 x 'A' and 2 x 'B') in the younger and older children enrolled in the study, the evaluator has a number of concerns:

- The study took place over just one NH season;
- The study enrolled predominantly children of white ethnicity, and hardly any children of Asian ethnicity were enrolled, this is of direct relevance to Australia;

- Overall, only 874 younger children (aged 5 to 8 years) have been exposed to Afluria Quad with all 4 strains split with higher levels of TDOC; do we know that future lots will be as immunogenic and safe?
- While Study CSLCT-USF-10-69 is a supportive study providing safety information without any immunogenicity data in the 5 to 8 year old age group, the TIV vaccine used in this study contained the H3N2 and B/Massachusetts/02/2012 (B Yamagata) strains split with higher concentrations of TDOC, the H1N1 strain was split with lower, more 'usual' concentrations of TDOC. While no safety signals of concern were revealed when comparing febrile reactions to historical data from older TIV formulations, these data would have been more compelling if the study was properly powered for the Comparator (a US registered QIV), and if the TIV vaccine had included all 3 strains split with higher concentrations of TDOC.
- The evaluator is aware that there is an ongoing study of Afluria Quad in children between the ages of 6 to 59 months, Study CSLCT-QIV-15-03, which is due to report in third Quarter of 2017. The safety and immunogenicity data for different lot(s) of Afluria Quad (containing A/California/7/2009 (H1N1); A/Hong Kong/4801/2014 (H3N2); B/Phuket/3073/2013 (B Yamagata); B/Brisbane/60/2008; (B Victoria)), albeit in a slightly younger age group, will provide further important data of this QIV in children, albeit in a younger age group. The evaluator thinks the data arising from Study CSLCT-QIV-15-03 will compliment that already provided in Study CSLCT-QIV-13-02 and provide a broader immunogenicity and safety profile in the paediatric.

First round recommendation regarding authorisation

The evaluator does not recommend authorisation.

Second round evaluation

The sponsor submitted further documentation. For details of the second round evaluation including the issues raised by the evaluator (clinical questions), the sponsor's responses and the evaluation of these responses, please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

Predicated upon further safety data as planned, including data from Study CSLCT-QIV-15-03, the benefit for the use of this QIV may be favourable in those aged 5 years and older.

Second round assessment of risks

As above, the sponsor has provided some reassurances in their response, including the lack of any safety concerns in Study CSLCT-QIV-15-03, but TGA will still need to review these data. This is planned in July 2017.

Second round assessment of benefit-risk balance

The evaluator may be in favour of benefit, predicated upon further safety data including data from Study CSLCT-QIV-15-03 indicating no concerning safety signal.

Second round recommendation regarding authorisation

No recommendation at this juncture; further safety data will be provided in the younger age group enrolled in Study CSLCT-QIV-15-03 to TGA in July 2017.[12]

VI. Pharmacovigilance findings

Risk management plan

Summary of RMP evaluation[13]

- The sponsor submitted EU-RMP version 5.0, 19 July 2017; data lock point (DLP) 21 May 2017 and ASA version 5.0, 22 June 2017, in the sponsor's post-first round evaluation response, in support of this application.
- The risk of off-label use in children requires additional pharmacovigilance and risk minimisation.
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised in Table 5, below.

Table 5: Summary of Safety Concerns.

Summary of Safety Concerns		Pharmacovigilance		Risk Minimisation	
		Routine (R)	Additional (A)	R	A
Important identified risks	Hypersensitivity (Anaphylaxis)	ü	-	ü	-
Important potential risks	Encephalomyelitis	ü	-	ü	-
	Seizures/convulsions	ü	-	ü	-
	Guillain-Barré syndrome	ü	-	ü	-
	Transverse myelitis	ü	-	ü	-
	Optic neuritis	ü	-	ü	-

[12] The interim results from Study CSLCT-QIV-15-03 were provided to TGA in July 2017 and are currently being evaluated as part of an application to extend the indication to children aged 6 months to 5 years of age.

[13] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of Safety Concerns		Pharmacovigilance		Risk Minimisation	
	Bell's palsy	ü	-	ü	-
	Serum sickness	ü	-	ü	-
	Off-label use in children < 5 years	ü	ü	ü	ü
Missing information	Use in children <5 years	ü	ü	ü	-
	Exposure and safety in pregnancy	ü	ü	ü	-
	Use in immunocompromised patients	ü	-	ü	-

- Additional pharmacovigilance activities include:
  - Pregnancy safety surveillance study (planned, US); registry or observational post-marketing safety surveillance study
  - Assessment of off-label use in children in Australia (ongoing) utilising reports provided by OHP
  - Study CSLCT-QIV-15-03 (ongoing, interim data provided);[14] Study to assess safety and tolerability of Seqirus QIV in children 6 months to < 5 years
  - Survey of HCP knowledge (ongoing); measure of effectiveness of the risk minimisation for off-label use in children
- Additional risk minimisation activities, to address the risk of paediatric off-label use include:
  - Dear Health Care Professional Letter
  - Electrostatic vaccine refrigerator sticker
  - ATAGI A5-size recommendation card with national recommendations for use.[15]

New and outstanding recommendations from second round evaluation

The recommendations made in the first round evaluation (Recommendations 1 to 8) have been addressed by the sponsor in their post-first round evaluation response.

The Afluria Quad RMP is generally acceptable but there is one outstanding recommendation for the safety specification and new advice to the Delegate regarding the contraindications in the PI.

Outstanding recommendation

- Recommendation 9: Vaccine failure must be included as an important potential risk and monitored by appropriate pharmacovigilance

[14] Additional data requested by the Delegate, submitted by the sponsor.
[15] ATAGI = Australian Technical Advisory Group on Immunisation

Other advice to the delegate

The sponsor has proposed to remove the contraindication for fever/acute infection, which is not acceptable. It is recommended to the Delegate that:

- Recommendation 9: The contraindication for fever/acute infection should be retained as follows: 'Immunisation should generally be postponed in individuals having a febrile illness or acute infection.' The CMI should also retain the relevant advice.

The Delegate's attention is drawn to the following amendments to the draft Product Information that were made by the sponsor, in response to RMP recommendations:

- Dosage advice has been formatted in a table
- Contraindication for individuals with hypersensitivity to egg was removed, to align with the Immunisation Handbook.

Proposed wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

- Implement Afluria Quad EU-RMP version 5.0, 19 July 2017; DLP 31 May 2017 with ASA version 5.0, 22 June 2017 and any future updates as a condition of registration.

VII. Overall conclusion and risk/benefit assessment

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

Quality

The data provided by the sponsor for the submission was considered in conjunction with the existing data previously reviewed. The approach taken in the quality evaluation was to summarise the available quality data – as it relates to the proposed change – and to identify the potential risks to quality and safety of the product for the proposed indicated group.

The sponsor has proposed a control strategy for release of the drug product into the proposed indicated population that appear to offer the potential to significantly reduce the risk of clinical outcomes similar to those of 2010 occurring with the current vaccine. An assessment of the success of the strategy is dependent on the generation of additional quality data from the forthcoming 2018 SH and 2018/19 NH influenza seasons and subsequent approval of the strategy by TGA. In the interim it is suggested that a condition of registration be placed upon the product to restrict release to those batches that meet a specification for total lipid content (expressed in µg/ml for the formulated drug product) and that are based on content of vaccines shown to have an acceptable safety profile in the indicated population. Of note, the conditions include:

- That the first three batches of final bulk vaccine for each seasonal product be tested in the NF-κB Activation Assay, and, that the assay be adapted to perform the testing under standard conditions and with at least one further dilution at a 4 fold increase in minimum concentration.

- That the lipid content for each strain be calculated (in mg/ml) for each batch of final bulk vaccine and that limits be applied to each type/subtype based on the lipid content levels determined for clinical trial lots.
- All independent batches of Afluria Quad are not released for sale until samples and the manufacturer's release data have been assessed and the sponsor has received notification acknowledging release from the TGA Laboratories Branch.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Study CSLCT-QIV-13-02 and Study CSLCT-USF-10-69 were evaluated in detail in the clinical evaluation report (CER) [see Attachment 2]. In order to provide background regarding the extension of indication to paediatric subjects, the summary of the 2010 SH reports of fever and febrile seizures in children receiving TIV in Australia and New Zealand and the company's scientific investigations into these adverse events were discussed, and the safety results from historical bioCSL TIV studies in children were briefly mentioned and compared.

Immunogenicity analysis from Study CSLCT-QIV-13-02

Study CSLCT-QIV-13-02 is a randomised, observer-blinded, comparator controlled study of bioCSL QIV, versus a US-licensed comparator QIV (Fluarix quadrivalent) containing the same influenza strains. The study was conducted during the 2015 to 2016 NH influenza season in subjects 5 to17 years of age. The primary objective(s) were to demonstrate that vaccination with bioCSL QIV (or called Seqirus QIV) elicits a non-inferior immune response to that of the comparator QIV containing the same virus strains. The non-inferiority of bioCSL QIV versus the comparator QIV was assessed by the 8 co-primary endpoints of HI GMT and SCR for each viral strain in the vaccines:

- 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 SCRs** for the A/H1N1 strain;
- The difference between the SCRs for the A/H3N2 strain;
- The difference between the SCRs for the B strain (Yamagata lineage);
- The difference between the SCRs for the B strain (Victoria lineage).

The key inclusion and exclusion criteria are described in the clinical evaluation report (CER). The test product is a single 0.5 mL dose of bioCSL QIV given IM. Each 0.5 mL dose contains 15 µg HA from each of the following 4 influenza strains; all 4 strains were split at the upper levels of TDOC concentration:

- 15 µg per 0.5 mL dose A/California/7/2009 (H1N1)pdm09-like virus;
- 15 µg per 0.5 mL dose A/Switzerland/9715293/2013 (H3N2)-like virus;
- 15 µg per 0.5 mL dose B/Phuket/3073/2013-like virus (B/Yamagata lineage);
- 15 µg per 0.5 mL dose B/Brisbane/60/2008-like virus (B/Victoria lineage).

The reference product is Fluarix quadrivalent (Fluarix QIV), administered as one 0.5 mL IM dose. Each 0.5 mL dose contains 15 µg HA from influenza strains which are the same as that in the test product. The study subjects were randomised using 3:1 ratio to bioCSL QIV or Fluarix QIV. Randomisation was stratified by age, that is, Cohort A = subjects 5 to 8 years of age; Cohort B = subjects 9 to 17 years of age. Quotas were applied to ensure ≥ 50% were in the younger age group. The subjects were scheduled to single vaccination or two-vaccination regimen as clinically indicated. The schedules of assessments and the analysis population are detailed in the CER [see Attachment 2]. The study was designed to achieve at least 80% power to show non-inferiority for all of the 8 co-primary endpoints using a one-sided alpha of 0.025 for each comparison. For comparisons of SCRs, a non-inferiority margin of 10% was employed. For comparison of GMT ratio, a non-inferiority margin of 1.5 was employed. This is in line with US influenza development guideline.[16]

The per protocol population was the primary analysis population for the primary immunogenicity analysis; a supporting analysis was performed using the evaluable population. If all 8 co-primary endpoints fulfilled non-inferiority criteria then overall non-inferiority of bioCSL QIV versus comparator QIV was concluded.

Secondary immunogenicity endpoints include GMT, SCR, SPR, and GMFI for the 4 influenza vaccine strains. Please see the CER for detailed participant flow and protocol deviations [available as Attachment 2]. The evaluable population = 2155 subjects within the Full Analysis Set who received study vaccine: 114 subjects excluded because either pre- and/or post-vaccination serology assay results were not available; another 6 were excluded because they had received ≥ 1 prohibited medications. Per protocol (PP) population included subjects in the evaluable population (n = 2155) minus subjects with protocol deviations assessed as potentially affecting the immunogenicity results (n = 22), hence the PP population = 2133 subjects.

No notable differences in demographic/baseline characteristics between the two groups in the FAS or within the age cohorts. Majority of subjects were White (73.3%); 20.7% subjects of black or African American origin. Mean (SD) age was 9.5 years. The age group balance remained within the rules set out in the protocol, with at least 50% in the 5 - 8 years of age stratum. In the FAS population, 51.19% (1166/2278) were in this age stratum. Of the 2278 in the FAS, 1998 subjects (87.7%) had previously received an influenza vaccine. 53.0% reported having received an influenza vaccine in the 2014/2015 NH Season. Percentages of subjects reporting having previously received an influenza vaccine were similar in the two age cohorts.

Results of the primary analysis

A total of 2275/2278 subjects (99.9%) received at least one vaccination with 2269/2278 subjects (99.7%) receiving vaccination according to protocol. A total of 293 subjects were assigned to 2 doses; 26 did not receive the 2nd vaccination and did not complete the study.

The primary analysis was completed using the PP population. Duplicate tables for the co-primary endpoints were also produced based on the evaluable population as there was a > 1% difference in the total number of subjects between the PP population and the evaluable population in the 5 to 8 years age group (1.67%). bioCSL QIV was shown to be non-inferior to the comparator QIV, with all 8 co-primary endpoints met for the 4 strains for GMTs and SCRs in subjects 5 to 17 years of age.

[16] Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines, Center for Biologics Evaluation and Research, 2007.

Table 6: Post-vaccination GMTs, SCRs, and Analyses of non-inferiority of bioCSL QIV relative to comparator QIV for each strain 28 days after last vaccination among children 5 -17 Years of age (per-protocol population)

Strain	Postvaccination GMT		GMT Ratio [a]	Seroconversion rate (SCR) % [b]		SCR Difference [c]	Met both pre-defined non-inferiority criteria? [d]
	bioCSL QIV (n=1605)	Comparator QIV (n=528)	Comparator QIV over bioCSL QIV (95% CI)	bioCSL QIV (n=1605) (95% CI)	Comparator QIV (n=528) (95% CI)	Comparator QIV minus bioCSL QIV (95% CI)	
A/H1N1	952.6 (n=1604 [e])	958.8	1.01 (0.93, 1.09)	66.4 (64.0, 68.7)	63.3 (59.0, 67.4)	-3.1 (-8.0, 1.8)	Yes
A/H3N2	886.4 (n=1604 [e])	930.6	1.05 (0.96, 1.15)	82.9 (81.0, 84.7)	83.3 (79.9, 86.4)	0.4 (-4.5, 5.3)	Yes
B/YAM	60.9 (n=1604 [e])	54.3	0.89 (0.81, 0.98)	58.5 (56.0, 60.9)	55.1 (50.8, 59.4)	-3.4 (-8.3, 1.5)	Yes
B/VIC	145.0 (n=1604 [e])	133.4	0.92 (0.83, 1.02)	72.1 (69.8, 74.3)	70.1 (66.0, 74.0)	-2.0 (-6.9, 2.9)	Yes

Source: [redacted] and [redacted].

Abbreviations: A/H1N1: A/California/7/2009 (H1N1) pdm09-like virus; A/H3N2 = A/Switzerland/9715293/2013 (H3N2)-like virus; B/YAM: B/Phuket/3073/2013-like virus (B/Yamagata lineage); B/VIC: B/Brisbane/60/2008-like virus (B/Victoria lineage); CI: confidence interval; GMT (adjusted): geometric mean titer. SCR: Seroconversion rate.

[a] GMT Ratio = Comparator QIV /bioCSL QIV. Adjusted analysis model: Log-transformed Post-Vaccination HI Titer=Vaccine + Age Strata [5-8, 9-17] + Gender + Vaccination History [y/n] + Log-transformed Pre-Vaccination HI Titer + Site + Number of Doses (1 vs 2) + Age Strata*Vaccine. The Age Strata*Vaccine interaction term was excluded from the model fit for the strains B/Yamagata and B/Victoria as the interaction result was non-significant (p>0.05). Least square means were back transformed.

[b] 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.

[c] Seroconversion rate difference = Comparator QIV SCR percentage minus bioCSL QIV SCR percentage.

[d] Noninferiority (NI) criterion for the GMT ratio: upper bound of two-sided 95% CI on the ratio of Comparator QIV /bioCSL QIV. GMT should not exceed 1.5. NI criterion for the SCR difference: upper bound of two-sided 95% CI on the difference between SCR Comparator QIV – bioCSL QIV should not exceed 10%.

Results for other immunogenicity outcomes

Secondary immunogenicity objectives were to characterise immunogenicity of bioCSL QIV and comparator QIV in two age strata, and overall. Immune responses were further characterised by SPRs, SCRs, and GMFIs by study vaccine and age cohort. Similar patterns of immune responses to those seen in subjects overall were seen within each of the two age strata for both study treatments. The post-vaccination GMTs for bioCSL QIV were higher for A than the B strains, and post-vaccination GMTs were similar between bioCSL QIV and Comparator QIV for all strains. GMFIs were similar for both age subgroups and both study vaccines. SCRs and SPRs were also similar for both age subgroups and both study treatments. Overall for bioCSL QIV, SCRs and SPRs were respectively: A/H1N1 66.4% and 99.7%, A/H3N2 82.9% and 99.4%, B/Yam 58.4% and 75.0% and B/Vic 72.1% and 90.3%. In general, male and female subjects showed similar pre- and post-vaccination GMTs and SCRs for both study vaccines. The study was not powered to allow comparisons between race and ethnic subgroups.

Safety

In 2010, bioCSL's SH TIV was associated with increased post-marketing reports of fever and febrile seizures in children. These reactions were predominantly in children 6 months to < 5 years of age. However, increased reports of febrile reactions compared with historical averages were also seen in children 5 to < 9 years of age. Since the 2010 SH influenza season, bioCSL TIVs, have not been approved for use in children < 5 years.

Before the 2010, bioCSL TIV was approved for use in children from 6 months of age in several countries globally. The 2010 SH paediatric AEs were initially detected in the 3rd year of a government sponsored paediatric influenza vaccination program in Western Australia (WA) in which bioCSL TIV was used. Research conducted in 2010 using in-vitro modelling in a subgroup of children ≤ 5 years with bioCSL TIV vaccine-related febrile convulsions, showed differences in cytokine production when peripheral blood mononuclear cells were stimulated with bioCSL TIV 2010 versus TIVs from other

manufacturers. This research demonstrated a potential clinical mechanism for the febrile AEs that is, a cytokine-mediated pyrogenic response.

An increased fever rate after receipt of 2009 bioCSL TIV compared to a US-licensed TIV among children 6 months to < 9 years was also observed in a clinical trial conducted in the US. The AE summary from this study for the two age groups 5 to < 9 years and 9 to < 18 years are also included in the US Afluria TIV label. After the 2010 event, bioCSL conducted intensive investigations to identify the cause of these AEs. Reports of the investigations have been published.[17] The conclusions from the investigations indicated that a combination of 3 key elements was predominant factors contributing to the 2010 SH paediatric AEs:

- Strain changes, in particular, replacement of all 3 virus strains in the 2009 SH vaccine formulation with the new strains for 2010 SH;
- Degraded RNA fragments that induced NF-κB, a key cellular transcription factor in cytokine production, and
- Conformation of heat-sensitive viral components, such as lipids, which appeared to facilitate RNA delivery.

Although the presence of RNA appears to be a contributing factor for the febrile reactions, its delivery is key to the induction of the cytokine/chemokine signal and this appears dependent on the lipid level present in the final formulation. The lipid content is inversely proportional to the concentration of the detergent TDOC used to disrupt the virus. Characterisation studies conducted examined the effect of varying TDOC concentration, used to split the virus during manufacture, on the NF-κB activation response. Reduction of lipids using the above process appears to reduce facilitated RNA fragment delivery into cells, decreasing the NF-κB induction associated with cytokine production. This may therefore reduce the potential for pyrogenic vaccine responses mediated by cytokines. During the investigations, the highest cytokine signal in the surrogate reactogenicity assays was generated by the B strain viruses, leading bioCSL to focus on splitting conditions for B strains. Based on the available data to date, the vaccine to be used in clinical trials starting from 2014, and in commercially supplied vaccines from 2014, will have the B strain split at the upper levels of TDOC concentration, which is within bioCSL's registered splitting range for TIV.

Safety analysis from Study CSLCT-QIV-13-02

The secondary objective(s) of this study were to assess safety and to characterise the immunogenicity of bioCSL QIV and the comparator QIV in children 5 to 17 years old. The exploratory objectives were to explore associations between any severe grade fever and other solicited systemic AEs after bioCSL QIV or the comparator QIV and to explore associations between immune response by vaccine dose and baseline characteristics. Please refer to the CER for the detailed safety analysis.

Overall, a total of 874 children 5 to 8 years and 834 children/adolescents 9 to 17 years received at least 1 dose of Afluria Quad. No deaths, adverse events of special interest (AESI), or AEs leading to withdrawal were reported in this study. Overall, 13 SAEs were reported in 10 subjects. Of these, 11 SAEs were reported in 8 subjects in the Afluria Quad group (0.5%) and 2 SAEs were reported in 2 subjects in the comparator QIV group (0.4%). One SAE (a cellulitis-like reaction) was experienced by a patient who received Afluria Quad. This subject experienced Grade 3 pain, Grade 3 swelling, and Grade 3 redness

[17] Rockman S, Dyson A, Koernig S, 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. 2014 Jun 24;32(30):3861-8; Rockman S, Becher D, Dyson A, et al. Role of viral RNA and lipid in the adverse events associated with the 2010 Southern Hemisphere trivalent influenza vaccine. Vaccine. 2014 Jun 24;32(30):3869-76.

concurrently from Day 3 to Day 7 after the first vaccination. The reaction was assessed by the Investigator and confirmed not to be cellulitis. All other SAEs were assessed as unrelated by the sponsor and the Investigator.

Solicited local adverse reactions were experienced by similar proportions of subjects in the two vaccine groups. The most common (≥ 10% of subjects) solicited local adverse reaction was pain at the injection site in both groups. In the 5 through 8 years age stratum, the proportion of subjects experiencing moderate and severe swelling at the injection site after any vaccination was slightly higher in the Afluria Quad group (7.0% and 3.4%, respectively) than in the comparator QIV group (4.0% and 2.2%, respectively). A similar pattern was observed for moderate and severe redness. Most of the solicited local adverse reactions (pain, redness and swelling), experienced in either vaccine group, started between Day 1 or Day 2 and had a mean duration of 1.6 to 1.8 days**.**

Most of the solicited systemic AEs were experienced by similar proportions of subjects in the two vaccine groups. The two most common (≥ 10% of subjects) solicited systemic AEs were headache and myalgia. In children 5 to 8 years of age, any fever and severe fever (≥39.0°C) was reported by 4.5% and 1.2% of subjects who received Afluria Quad and by 3.6% and 0.7% of subjects who received Comparator QIV, respectively. In children 9 - 17 years of age, fever was experienced by 2.1% who received Afluria Quad and by 0.8% who received Comparator QIV. Severe fever was experienced by 0.5% in the Afluria Quad group. There were no severe fevers experienced in the Comparator QIV group. A statistically significant relative risk (RR) was observed only for myalgia in subjects the 9 through 17 years age stratum vaccinated with Afluria Quad (RR: 1.5, 95% CI; 1.03, 2.19). The proportion of subjects vaccinated with Afluria Quad who experienced any solicited systemic symptom was higher in the 9 through 17 years age stratum (34.1%), compared with the 5 through 8 years age stratum (27.6%), with headache and myalgia most commonly reported in both age strata.

No unsolicited AE was reported by > 10% subjects in any vaccine group or age stratum. The most common unsolicited AE (≥ 1 % overall subjects) reported by subjects was cough (2.0%), reported by similar proportions of subjects in both vaccine groups (Afluria Quad 2.1%, comparator QIV: 2.0%). The other common unsolicited AEs reported in subjects overall were pyrexia (1.4%), oropharyngeal pain (1.3%), and vomiting (1.0%). Other unsolicited AEs reported by ≥ 1 % subjects in any vaccine group included upper respiratory tract infection (Afluria Quad: 1.1%), ear pain (Comparator QIV: 1.1%), and rhinorrhoea (comparator QIV: 1.1%).

Relatively small numbers of subjects received a second vaccine, there was no evidence that receipt on the second vaccine was associated with an excess of solicited local and systemic side-effects, or unsolicited AEs; in general the second vaccine was better tolerated.

In summary, the study showed that Afluria Quad and the Comparator QIV were generally well tolerated with similar safety profiles.

Safety data from Study CSTCT-USF-10-69

The Fluvax TIV is approved in children and adolescents ≥ 5 years of age. Due to concerns over pyrogenicity in children < 5 years of age, Seqirus conducted a small safety study (Study CSLCT-USF-10-69) of the TIV in children 5 to 8 years of age concurrent with the QIV adults study (Study CSLCT-QIV-13-01). Because Study CSLCT-USF-10-69 demonstrated acceptable safety including less pyrogenicity than in prior studies, CBER agreed that plans for a larger study of Afluria QIV in children 5-17 years of age (Study CSLCT-QIV-13-02) could proceed.

Study CSLCT-USF-10-69 is a randomised, observer-blind, comparator-controlled, multicentre study. The primary objective was to evaluate safety and tolerability of Seqirus

TIV in children 5 to 8 years of age. It was primarily conducted to provide contemporary data on safety and tolerability of Seqirus TIV manufactured with higher TDOC splitting conditions for the B strain, to inform the design and conduct of planned Seqirus QIV clinical development in children. The trial vaccine was Seqirus TIV (2014 to 2015 NH season formulation, H3N2 and B strains were split with higher concentrations of w/v TDOC). Comparator vaccine was Fluzone Quadrivalent.

Subjects received one or two vaccinations depending on their influenza vaccination history. A single study vaccination was scheduled if the subject received ≥ 2 seasonal influenza vaccinations since July 2010. Subjects were randomised to one of the two treatment groups in a 3:1 ratio (Seqirus TIV: Comparator QIV). The study was not powered to allow direct comparison between the two study vaccines. Subject disposition and statistical methods were descriptive only. In total there were 292 children aged 5 to 8 years in the safety analysis set for 1st vaccination.

There were no deaths or AEs leading to study withdrawal, no AEs triggering the halting rules in either vaccine group. One SAE (severe delirium febrile) occurred on Day 3 post Seqirus TIV and was resolved the same day. The SAE was assessed as 'listed/expected' and vaccine related. Although the event of 'delirium febrile' did not meet halting criteria at the time and did not trigger study halt, the Data and Safety Monitoring Board (DSMB) Chair was notified of the event via email communication one day after initial receipt of the SAE.

Solicited local AEs occurred in most subjects and were of mild intensity. A higher proportion reported local AE after the first vaccination in both vaccine groups. Most local AE reported after Seqirus TIV started on Day 1 and lasted 1- 2 days. Mean duration of pain, redness and swelling was longer following the first vaccination compared with the second in both vaccine groups. In the comparator QIV group, most reactions started on Day 1 and lasted 2 to 3 days. The most common solicited local AE was pain and persisted for a mean duration of 2 days in both vaccine groups.

Solicited systemic AEs occurred in 40.8% of subjects in Seqirus TIV group and 44.9% in comparator QIV group. A higher proportion of subjects reported solicited systemic AEs after the first vaccination. The most common solicited systemic AE was myalgia and headache. Malaise and diarrhoea more commonly reported (by >10% subjects) in the comparator QIV group. Most solicited systemic events reported by Seqirus TIV group began on/after Day 2 (except myalgia, which started on Day 1) and lasted 1-2 days. Average onset day for solicited systemic AEs was Day 1, 2 or 3 (myalgia and diarrhoea: average onset Day 1; headache, malaise & vomiting: average onset Day 2; nausea & fever: average onset Day 3). The duration of events was slightly longer after comparator QIV (1 to 3 days).

The fever rates were similar between the vaccine groups. The overall fever rate (during 7 days after vaccination) with Seqirus TIV was 8.2%; most fever event(s) were considered related. Severe fever event(s) occurred in 2.1% of subjects and related severe fever event(s) occurred in 1.7% of subjects. In the comparator QIV group, the overall fever rate was 9.2%; severe fever: 4.1%; related fever: 5.1%; severe related fever: none reported; Exploratory analyses were performed with adjustment for covariates including age, sex, weight, vaccine dose or previous vaccination in order to evaluate the contribution of these factors to fever outcomes, no association was found.

Unsolicited AEs experienced within 7 days post-vaccination reported in 14.0% in Seqirus TIV group and 22.4% in comparator QIV group. Cough was more commonly reported (4.1%) in the Seqirus TIV group and oropharyngeal pain and abdominal pain more commonly reported (3.1%) with comparator QIV. Higher proportions reported unsolicited AEs after 1st versus 2nd vaccination in both vaccine groups.

In summary, the study showed that vaccination with both Seqirus TIV and comparator QIV were generally well tolerated with similar safety profiles in subjects 5 through 8 years of age.

Concerns raised by the evaluator at first round

While the data arising from Study CSLCT-QIV-13-02 demonstrate that Afluria Quad appears to have an acceptable safety and immunogenic profile against all 4 influenza strains in the younger and older children enrolled in the study, the clinical evaluator has raised the following concerns:

- Study CSLCT-QIV-13-02 took place over just one NH season; and this study enrolled predominantly children of white ethnicity, and hardly any children of Asian ethnicity were enrolled, this is of direct relevance to Australia;
- Overall, only 874 younger children (aged 5-8 years) have been exposed to Afluria Quad with all 4 strains split with higher levels of TDOC, it is not known that if the future lots will be as immunogenic and safe.
- Study CSLCTUSF-10-69 is only a supportive safety study in the 5 to 8 year old age group, the TIV vaccine used in this study contained the H3N2 and B/Massachusetts/02/2012 (B Yamagata) strains split with higher concentrations of TDOC, the H1N1 strain was split with lower concentrations of TDOC. While no safety signals were revealed when comparing febrile reactions to historical data from bioCSL TIV, these data would have been more compelling if the study was properly powered for the Comparator (a US registered QIV), and if the TIV had included all 3 strains split with higher concentrations of TDOC.
- There are limited or no data in immunocompromised patients and in Australian indigenous ethnicity.

Post-first round evaluation response submitted by the sponsor

In the response the sponsor provided a comprehensive of quality assurance that includes targeted splitting of all influenza strains included in QIV with higher concentrations of TDOC, and a control strategy to ensure optimised lipid clearance. The sponsor also states that Afluria Quad will not be marketed in Australia with an indication of 5 years and above until 2019 SH influenza season, in which time the sponsor will have accumulated one seasons' post-marketing reports generated from the US NH 2018/19 season. In addition, the sponsor states that they will conduct enhanced safety surveillance for reactogenicity in Australia if deemed necessary or requested by TGA.

The sponsor also states that Study CSLCT-QIV-15-03, a study of Afluria Quad in children between the ages of 6 to 59 months, has completed enrolment and the active study period, the immunogenicity data, solicited and unsolicited data has been collected. The study is in follow-up to collect all SAE through to the 180 days post vaccination. The sponsor later presented the interim safety results of this study to TGA.

The sponsor also states that Study CSLCT-QIV-15-03, a study of Afluria Quad in children between the ages of 6 to 59 months, has completed enrolment and the active study period, the immunogenicity data, solicited and unsolicited data has been collected. The study is in follow-up to collect all SAE through to the 180 days post vaccination. The sponsor later presented the interim safety results of this study to TGA.

Interim safety results from Study CSLCT-QIV-15-03

The interim results of Study CSLCT-QIV-15-03 (Interim data lock: 8 May 2017) was presented to TGA during July 2017. The sponsor also provided TGA with a copy of the FDA

meeting package which contained more detailed immunogenicity and safety summaries of this study.

Study CSLCT-QIV-15-03 was a randomised, observer blind, comparator controlled trial conducted in the U.S. in 2247 subjects aged 6 through 59 months. Subjects were stratified into one of two age cohorts of 6 through 35 months or 36 through 59 months. Subjects in the safety population (N = 2232) received either Afluria Quadrivalent (N = 1673) or a US-licensed comparator QIV Fluzone Quadrivalent (N=559). Study subjects were scheduled to receive either a single vaccination or two vaccinations 28 days apart based on their previous vaccination history. The study showed that immunogenicity of Afluria Quad in children 6 through 59 months of age was non-inferior to the QIV comparator based on the adjusted GMT ratios and seroconversion.

The secondary safety endpoints in Study CSLCT-QIV-15-03 were the frequency and severity of solicited local adverse reactions and systemic adverse events (AEs) for 7 days after each vaccination dose, cellulitis-like reactions and unsolicited AEs for 28 days after each vaccination dose, and SAEs for 180 days after the last vaccination for each age cohort and overall.

The safety analysis showed that the proportion of subjects 6 through 35 months of age with any solicited local adverse reaction following any vaccination was similar in the two study vaccine groups. The most common local adverse reaction experienced were injection site pain followed by injection site redness. Injection site swelling was experienced by < 10% of subjects. For subjects 36 through 59 months of age, the proportion of subjects with any solicited local adverse reaction following any vaccination was also similar in the two study groups. The most common local adverse reaction experienced was injection site pain. Injection site redness and swelling were experienced by > 10% of subjects. Most local adverse reactions in both age cohorts were mild in intensity. Moderate and severe redness and swelling were reported by fewer subjects in the Afluria Quadrivalent group than in the Comparator QIV group in the 36 to 59 months age group.

The proportion of subjects 6 through 35 months of age with any solicited systemic adverse event following any vaccination was similar in the two study vaccine groups (Afluria Quadrivalent: 48.9%, comparator QIV: 49.8%). The most common systemic adverse event experienced was irritability. Diarrhoea and loss of appetite were experienced by more than 10% of subjects. Nausea and vomiting was experienced by less than 10% of subjects for Afluria Quadrivalent at 9.4%, and comparator QIV at 11.0%. Fever was experienced by <10% of subjects in the Afluria Quadrivalent vaccine group (7.0%, comparator QIV: 11.9%). The proportion of subjects experiencing fever was significantly lower in the Afluria Quadrivalent group than in the comparator QIV group (Relative Risk: 0.59, 95% confidence interval: 0.38; 0.93). Severe fever (≥ 102.2°F/ ≥ 39.0 °C) was reported in similar frequencies in both vaccine groups (Afluria Quadrivalent: 2.5%, comparator QIV: 2.6%).

For subjects 36 through 59 months of age, the proportion of subjects with any solicited systemic adverse event following any vaccination was similar in the two study vaccine groups. The most common systemic adverse events experienced by > 10% of subjects were malaise and fatigue, and diarrhoea. Fever was experienced by < 10% of subjects and in similar frequencies in both vaccine groups (Afluria Quadrivalent: 4.8%, comparator QIV: 6.0%). Severe fever (≥ 102.2°F/ ≥ 39.0°C) was experienced by 1.2% of Afluria Quadrivalent subjects and 0.9% of comparator QIV subjects.

Most systemic adverse events in both age cohorts were mild in intensity.

A similar proportion of subjects 6 through 59 months of age experienced one or more unsolicited adverse events (UAE) in the two vaccine groups. Less than 10% of subjects experienced UAEs that were considered related to study vaccine by the investigator. Most

related UAEs were mild in intensity. Rhinorrhoea was the most commonly reported related UAE for Afluria Quadrivalent at 2.2%. All other related UAEs were reported by less than 2% of subjects.

No AEs of special interests were reported in any subjects up to the Study Exit Visit, but there was one febrile convulsion reported after the Study Exit Visit. This event occurred on Day 43 in a patient who received Afluria Quadrivalent. The event was assessed as unrelated to the study vaccine due to the time between vaccination and the event and the presence of an upper respiratory infection for 2 weeks preceding one episode of simple febrile convulsion. The subject did not experience fever 7 days following vaccination with Afluria Quadrivalent. There were no reports of cellulitis-like reaction with Afluria Quadrivalent, and one report in a subject who received Comparator QIV. Of the 5 SAEs reported by 4 subjects up to Day 28, none were assessed as related to the study vaccines. SAEs were reported for an additional 8 subjects (6 in the Afluria Quadrivalent group and 2 in the comparator QIV group) between Day 29 and the interim database lock; all were assessed as unrelated to vaccination. The majority of SAEs were in the System Organ Class (SOC) infections and infestations.

Safety analysis showed that the Afluria Quadrivalent safety profile is similar to Fluzone Quadrivalent. The safety profile of Afluria Quadrivalent in subjects 6 through 59 months of age is considered acceptable.

Risk management plan

The sponsor submitted EU-RMP version 5.0, 19 July 2017; DLP 21 May 2017 and ASA version 5.0, 22 June 2017, in the Section 31 response, in support of this application.

It is noted that Seqirus has updated the ASA to include the following text:

> *Conduct enhanced safety surveillance (ESS) for Afluria Quadrivalent in Australia, as deemed necessary or requested by TGA*

Seqirus further states that the proposed ESS will be similar to that conducted annually in Europe for Seqirus TIV (Enzira) in accordance with Interim Guidance on Enhanced Safety Surveillance (ESS) for seasonal influenza vaccines in Europe. A brief description of the ESS plan is provided in the updated ASA. If conduct of an ESS is deemed necessary by the TGA, Seqirus commits to submit the full description of the ESS plan to TGA and conduct the ESS.

It is noted that the sponsor has committed to revise the PI and ASA as per recommendation.

Wording for conditions of registration:

> *Implement Afluria Quad EU-RMP version 5.0, 19 July 2017; DLP 31 May 2017 with ASA version 5.0, 22 June 2017 and any future updates as a condition of registration.*

Risk-benefit analysis

Delegate's considerations

The pivotal Study CSLCT-QIV-13-02 used the immunogenicity endpoints as surrogate endpoints for clinical efficacy. This is a standard approach in influenza vaccine studies. The non-inferiority of Afluria Quad versus a US-approved QIV was demonstrated through the 8 co-primary endpoints of GMT and SCR for each viral strain.

Study CSLCT-QIV-13-02 provided **s**afety data for Afluria Quad in the proposed age group. This study was conducted during the NH 2015 to 2016 season. In total, 874 children aged 5 to 8 years and 834 children/adolescents aged 9 to 17 years received at least 1 dose of

Afluria Quad. Fever rates were comparable to the QIV comparator in both age groups. In children 5 to 8 years of age, any fever and severe fever was reported by 4.5% and 1.2% of subjects who received Afluria Quad and by 3.6% and 0.7% of subjects who received comparator QIV, respectively. In children 9 to 17 years of age, fever was experienced by 2.1% who received Afluria Quad and by 0.8% who received comparator QIV. Severe fever was experienced by 0.5% in the Afluria Quad group. There were no severe fevers experienced in the comparator QIV group.

Study CSLCT-USF-10-69 provided the safety data for Seqirus TIV (2014-2015 NH season), in which the H3N2 and B strains were split with a higher TDOC concentration. In total there were 292 children (5 to 8 years) in the safety analysis set for first vaccination. The study was underpowered for a proper comparison with the Comparator QIV. Overall fever rate and severe fever rate was 8.2% and 2.1%, respectively with Seqirus TIV. Similar rates were observed in the comparator QIV group with an overall fever rate and severe fever rate of 9.2% and 4.1%, respectively. Fever events deemed related occurred in 7.5% recipients of Seqirus TIV and 5.1% recipients of comparator QIV. Severe related fever events occurred in 1.7% of subjects vaccinated with Seqirus TIV versus none with comparator QIV. Vaccination with Seqirus TIV and Comparator QIV was generally safe and well tolerated.

In previous paediatric studies of bioCSL TIV, the proportion of subjects 5 to 8 years of age who reported fever was between 9.8% and 16.2%. Based on 300 subjects in the bioCSL TIV group, if the rate was observed to be 16% the width of a 95% CI was to be 8.5%. When comparing with the historical fever rates in previous paediatric studies (Studies CSLCT-USF-07-36, CSLCT-USF-06-29 and CSLCT-FLU-04-05) in the same age group, overall and severe fever rates were lower in children vaccinated with the Seqirus TIV (2014 to 2015 NH season) in Study CSLCT-USF-10-69 (the H3N2 and B strains were split with higher concentrations of TDOC).

The data from Study CSLCT-QIV-15-03 provide the safety and immunogenicity data for a different batch of Afluria Quadrivalent in a younger age group. Based on the study summary provided to the TGA, the immunogenicity and safety results are reassuring.

The sponsor has made a commitment to conduct enhanced passive safety surveillance if deemed necessary or requested by the TGA. In addition, the sponsor proposes to market Afluria Quad with an indication of 5 years and above in the SH 2019 influenza season, once indication alignment for the private and NIP supplied product can be met. From SH 2019, the sponsor proposes to provide updated risk minimisation materials to communicate the age indication of Afluria Quad vaccine and minimise the risks of potential off-label use in children less than 5 years of age. The proposal to market Afluria Quad for an indication of 5 years and above in the SH 2019 season would allow time for the sponsor to accumulate one seasons' post-marketing reports from the US NH 2018/19 season.

Summary of issues

Study CSLCT-QIV-13-02 was conducted over one NH season. In total, 874 children aged 5 to 8 years and 834 children/adolescents aged 9 to 17 years received at least 1 dose of Afluria Quad. In this study, Afluria Quad with all 4 strains was split with higher levels of TDOC. The study showed that Afluria Quad and the comparator QIV (Fluarix quadrivalent) were generally well tolerated with similar safety profiles.

Study CSLCT-USF-10-69 provided safety data for the use of the sponsor's TIV in the 5 to 8 year old age group. The study was not powered to allow direct comparison between the sponsor's TIV and Fluzone Quadrivalent. In total there were 292 children aged 5 to 8 years in the safety analysis set for first vaccination. The study showed that vaccination with Seqirus TIV and Fluzone Quadrivalent were generally well tolerated with similar safety profiles in subjects 5 through 8 years of age.

The interim data from Study CSLCT-QIV-15-03 was provided to TGA. A different batch of Afluria Quad was studied in 6 months to 5 years old age group in this study. Safety analysis showed that the Afluria Quadrivalent safety profile is similar to Fluzone Quadrivalent in subjects 6 through 59 months.

Request for ACV advice[18]

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

- Does the ACV consider that the submitted data are adequate to support the extension of indication to include the age group of 5 to 17 years old?
- What is the advice of the ACV with regards to the post-market safety surveillance for the use of Afluria Quad in the 5 to 17 years old?
- Could ACV please comment on the AusVaxSafety program? Is AusVaxSafety considered as adequate active post-market safety surveillance for the vaccines included in the National Immunisation Program?

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.

Pre-ACV assessment

Pending the ACV advice, the Delegate is proposing the registration approval for the extension of indication to include 5 to 17 year age group. In addition to the conditions proposed by Quality evaluator, an updated RMP must be provided for TGA review prior to marketing of Afluria Quad with the indication of > 5 years old, and the updated RMP must include the following:

- Updated safety information, including the post-marketing safety data in 5 to 17 years age group from the US NH 2018/19 season.
- Updated risk minimisation materials for SH 2019 to communicate the age indication of Afluria Quad and minimise the risks of potential off-label use in children less than 5 years of age.
- Adequate post-market safety surveillance plan in Australia to detect early safety signal for the use of Afluria Quad in 5-17 year old in the SH 2019 season.

Response from sponsor

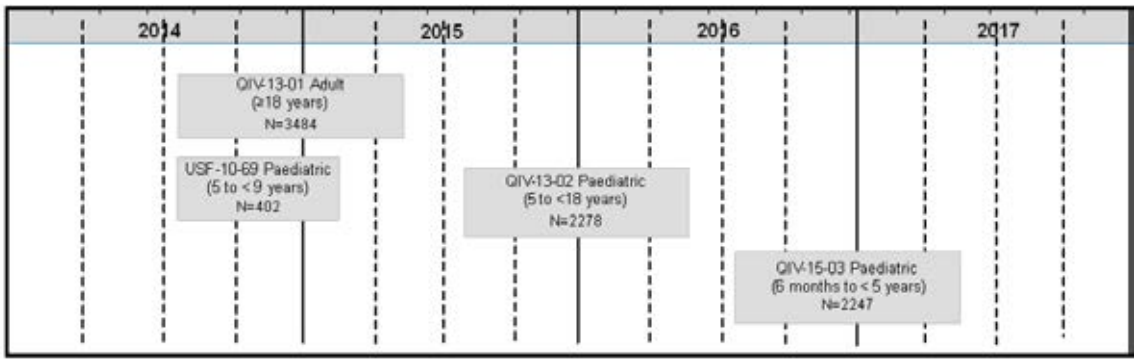
Seqirus appreciates the opportunity to respond to the TGA's Request for ACV advice. The sponsor welcomes the Delegate's preliminary assessment that there are no reasons precluding approval for the proposed indication for the sponsor's quadrivalent seasonal influenza vaccine (QIV), Afluria Quad, to be used in persons aged 5 years and older. The US FDA also reached the same conclusion and approved Afluria Quadrivalent for use in persons aged 5 years and older on 31 August 2017.

Delegates summary of issues

The Delegate indicates that Study CSLCT-QIV-13-02 was conducted over one NH season. As described by the sponsor, the paediatric clinical development programme for Afluria Quad was designed to characterise the safety and tolerability of the vaccine in the paediatric population of 6 months to < 18 years in a phased and reinforcing manner over a number of consecutive NH seasons as shown below.

[18] ACV = Advisory Committee on Vaccines

Figure 1: Seqirus influenza vaccine clinical development programme.



The paediatric clinical programme was conducted over three different seasons using three different vaccine lots and includes a supportive safety study of the trivalent (TIV) formulation in children 5 to < 9 years (Study CSLCT-USF-10-69) and two pivotal studies using the quadrivalent formulation of the vaccine in children 5 to < 18 years (Study CSLCT-QIV-13-02) and in children 6 months to < 5 years (Study CSLCT-QIV-15-03).

In the two QIV paediatric studies, a total of 3365 subjects aged < 18 years, 75% (2547 subjects) of whom were aged < 9 years, contributed immunogenicity and safety data in support of Afluria Quad. The clinical programme design ensured exposure in younger subjects was adequately represented. The studies have demonstrated a non-inferior immunogenic response and a clinically acceptable and comparable safety and tolerability profile with the US-licensed comparators (equivalent to currently licensed influenza products in Australia).

These data support the view that individual lots over multiple seasons have an acceptable immunogenicity and safety profile in children under 18 years of age.

The Delegate also comments that Study CSLCT-USF-10-69 was not powered to allow direct comparison of safety data in the 5 to < 9 year old age group between Seqirus' TIV and Fluzone Quadrivalent. Study CSLCT-USF-10-69 was designed as a safety study to characterise fever and fever events in a dataset of at least 300 subjects receiving Seqirus TIV. The sample size of 300 was adequate to detect commonly occurring AEs such as fever and the results informed the decision to proceed with the paediatric Afluria Quad studies. The comparator vaccine was included as a reference but not for the purpose of comparison. Study CSLCT-QIV-13-02 was sufficiently powered to compare the immunogenicity and safety with a licensed QIV.

Concerns raised by the evaluator at the first round evaluation

The clinical evaluator raised no formal clinical questions and concluded that the immunogenicity of Afluria Quad in children 5 to < 18 years of age was non-inferior and the safety profile was similar to the comparator. The sponsor addressed the clinical evaluator's potential concerns in the response to the TGA's post-first round evaluation requests. In regard to the generalisability of clinical data to additional sub-groups (including race and ethnicity), the sponsor is not aware of an available body of evidence from inactivated influenza vaccine studies that suggests that race or ethnicity is a clinically significant independent factor on the immunogenicity or safety and tolerability of these vaccines in any particular age group. Additionally, in relation to limited data in immunocompromised patients, the sponsor designed the clinical studies to be inclusive of subjects with co-morbid conditions, provided that the conditions were neither severe nor recently unstable. The clinical data are therefore considered to be broadly representative of subjects that are likely to be vaccinated in Australia.

The sponsor would like to note that Afluria Quad will not be marketed in Australia for the 5 to < 18 year age indication until the SH 2019 season, to ensure alignment of the age

indication in the private market and the National Immunisation Programme. Data from post-marketing reports for Afluria Quad in children 5 to < 18 years following the US NH 2018 to 2019 season will be monitored to ensure that data gathered in Study CSLCT-QIV-13-02 study are generalisable to a broader population.

Response to quality evaluation

Concurrent with the phased QIV clinical development programme, the sponsor has implemented a multi-layered quality controls which serves to assure the quality and safety of Afluria Quad. The foundations of the Quality Control Strategy are the learnings from the scientific investigations into the adverse events associated with the 2010 SH trivalent influenza vaccine (TIV).[19] The strategy has incorporated a higher concentration of the detergent TDOC for splitting all virus strains to be included in the vaccine formulation. Quality data generated to date demonstrate that the implementation of a higher concentration of TDOC for virus splitting provides lipid clearance to a level that ensures complete abrogation of signal in the NF-κB activation assay (a surrogate in vitro assay for inflammatory cytokine-mediated reactogenicity).[20]

Another key component of the quality control strategy is the screening of all new strains to determine their suitability. Screening occurs at pilot scale and for the first three monovalent pooled harvest (MPH) production scale batches and includes NF-κB activation and lipid content assays to demonstrate that the level of TDOC used limits potential reactogenicity.

To further enhance this strategy for the intended indication, and as referenced by the Delegate, Seqirus has committed to generate additional supportive quality data during the SH 2018 and NH 2018 to 2019 seasons (depending on strain changes). As Afluria Quad will not be marketed in Australia for the intended indication until the SH 2019 season, this will enable assessment of the additional quality data being generated during the SH 2018 season in support of the sponsor's quality control strategy to ensure the continued quality and alignment with the safety profile of Afluria Quad.

In the interim, whilst this data is being generated, the Delegate has suggested that three conditions of registration be placed upon the product indicated for use in persons aged 5 years and older. The sponsor's responses to these suggested interim conditions of registration are provided as follows.

Testing the first three batches of final bulk vaccine by the NF-κB activation assay

As suggested by the Delegate, and as previously committed in the sponsor's response to the TGA's post-first round requests, the sponsor agrees that the first three lots of final bulk vaccine manufactured (following the introduction of any new working seed lot) for each seasonal product will be tested in the NF-κB Activation Assay. The sponsor also agrees that the assay be adapted to perform the testing under standard conditions and with at least one further dilution at a minimum 4 fold increase in concentration provided that this concentration does not compromise the performance of the assay.

Calculation of lipid content in the drug product with limits to be applied per type/subtype

The sponsor acknowledges the Delegate's suggestion that the lipid content for each strain be calculated (in µg/ml) for each batch of final bulk vaccine and limits be applied to each type/subtype.

[19] Further information regarding the outcomes of the scientific investigations into the adverse events associated with the 2010 SH TIV is given in the Delegate's request for ACV advice.
[20] Rockman et al. Role of viral RNA and lipid in the adverse events associated with the 2010 Southern Hemisphere trivalent influenza vaccine. Vaccine, 2014 32(30):3869–3876.

The limit values are the lipid content from each influenza strain used in the formulation of the vaccine used in the paediatric clinical study in children 6 months through 59 months (Study CSLCT-QIV-15-03). The interim results of Study CSLCT-QIV-15-03 were presented to the TGA in a face to face meeting on 20 July 2017.[21] As stated by the Delegate, safety analysis showed that the safety profile of Afluria Quadrivalent is similar to that of Fluzone Quadrivalent (equivalent to FluQuadri) in subjects 6 through 59 months of age and that the safety profile of Afluria Quadrivalent in subjects 6 through 59 months of age is considered acceptable.

The calculated total lipid content of the vaccine used in Study CSLCT-QIV-15-03 in children 6 months through 59 months was higher than that used in the clinical study for the intended indication in persons 5 to 17 years of age (Study CSLCT-QIV-13-02), but within the range typically encountered as a result of batch-to-batch and strain-to-strain variation. As the younger age cohort is more sensitive to febrile reactions, the total lipid content of the vaccine that was used in Study CSLCT-QIV-15-03 is considered to represent the most appropriate and clinically-relevant safety threshold for lipid content at the current time.

While Seqirus agrees that an interim lipid content specification is applied to the drug product to be marketed for the indicated population, Seqirus does not agree that specifications be applied per influenza type/subtype. The sponsor's experimental data indicate that total lipid content is a contributing factor to potential cytokine-mediated reactogenicity and not the lipid level of each individual influenza type/subtype. Therefore, it is more appropriate to apply an interim specification limit for the total lipid content to the final bulk vaccine (drug product).

The sponsor's experimental data, published by Rockman et al.,[22] have shown that the induction of an NF-κB signal is the result of the cumulative lipid content contribution of each strain included in the vaccine (that is, the total lipid content) and that the relative contribution of each strain is not synergistic. Furthermore, these data show that an exogenous (non-viral) lipid source can be substituted for viral lipid to induce an NF-κB signal in the presence of viral RNA (extracted from the sponsor's 2010 trivalent influenza vaccine) which without lipid does not induce a signal.

Characterisation of the drug product lipid content for QIV development lots, QIV clinical trial lots, and SH 2017 and NH 2016 to 2017 commercial lots demonstrates that all vaccine lots manufactured to date contain a total lipid content with satisfactory batch-to-batch consistency.

The sponsor is committed to providing a vaccine with an acceptable safety and efficacy profile for the Australian public and Seqirus will request further TGA consultation regarding the proposed conditions of registration, to ensure that the most appropriate and clinically-relevant safety threshold for lipid content is implemented as a condition of registration.

Release for sale

In accordance with TGA's batch release processes, the sponsor agrees that all independent batches of Afluria Quad are not released for sale until samples and the manufacturer's release data have been assessed and the sponsor has received notification acknowledging release from the TGA Laboratories Branch.

[21] As referenced by the Delegate, the FDA meeting package containing a detailed immunogenicity and safety summary for study CSLCT-QIV-15-03 has been provided by TGA for ACV information.
[22] Rockman et al. Role of viral RNA and lipid in the adverse events associated with the 2010 Southern Hemisphere trivalent influenza vaccine. Vaccine, 2014 32(30):3869–3876.

Conclusion

The data presented by the sponsor demonstrates that Afluria Quad is immunogenic (by non-inferiority) and has an acceptable safety profile in children aged 5 to < 18 years. The sponsor concurs with the Delegate's conclusion that there are no reasons precluding approval for the proposed indication for Afluria Quad to be used in persons aged 5 years and older.

Advisory Committee Considerations[23]

The Advisory Committee on Vaccines (ACV) provided advice on Afluria Quad during the October 2017 ACV meeting. Following liaison between TGA and the sponsor, the sponsor provided a justification for a clinical study and an outline of the study. The study will essentially collect the same data in a clinical trial as was recommended by the ACV to be collected in post-market surveillance, in a higher risk patient group (younger children). The documents were provided to the committee for information.

The ACV, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

- Given the ACV's uncertainty about the safety of this vaccine in 5 to 17 years age group, the ACV would only support registration if the following commitments by the sponsor were met as conditions of registration:

  1. a commitment to conduct enhanced [active][24] post-market safety surveillance for fever and other Adverse Events of Interest (refer to EMA/PRAC/222346/2014);[25] over additional seasons and between different vaccine batches
  2. a commitment to implement process controls on the ~~total~~[26] lipid content for the individual influenza B strains, as well as total lipid content, with the maximum limit set at concentrations consistent with those from pre-marketing studies.

As a minimum, enhanced post-authorisation safety surveillance based on active follow up of vaccinated children should be conducted according to EMA guidance. For each vaccine batch at least 100 children aged 6 to 12 and another 100 children aged 13 to 17 should be actively followed up. This should involve at least 3 vaccine batches in each season and at least 3 separate seasons. The sponsor should carefully choose a region where the vaccine is highly likely to be used first, and where this enrolment is likely to be achievable within one month (refer to EMA/PRAC/222346/2014).[27] The protocol should be agreed between the sponsor and TGA.

This should be complemented by enhanced passive surveillance such that the proportion of vaccinated individuals with reported adverse events can be estimated (that is, where denominator data are available). While an indication for children < 5 years is not currently

[23] The ACV provides independent medical and scientific advice to the Minister for Health and TGA on issues relating to the safety, quality and efficacy of vaccines supplied in Australia including issues relating to pre-market and post-market functions for medicines. The Committee is established under Regulation 35 of the *Therapeutic Goods Regulations 1990*. Members are appointed by the Minister. Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

[24] This word has been added for clarity. It was not initially included in the version provided to the sponsor in October 2017. 'Active follow-up' does occur in the next paragraph, and the complementary role of 'passive surveillance' is stated in the final paragraph.

[25] EMA/PRAC/222346/2014: Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU.

[26] This word has been removed for clarity. It was initially included in the version provided to the sponsor in October 2017.

[27] EMA/PRAC/222346/2014: Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU.

being sought, safety data in this age group in ongoing studies should be made available when complete.

Post Advisory Committee considerations

RMP

The sponsor needs a commitment to conduct post-market safety surveillance for fever and other AESI over additional seasons and between different vaccine batches.[28]

As a minimum, enhanced post-authorisation safety surveillance based on active follow up of vaccinated children should be conducted according to EMA guidance. For each vaccine batch, at least 100 children aged 6 to 12 and another 100 children aged 13 to 17 should be actively followed up. This should involve at least 3 vaccine batches in each season and at least 3 separate seasons. The sponsor should carefully choose a region where the vaccine is highly likely to be used first, and where this enrolment is likely to be achievable within one month (refer to EMA/PRAC/222346/2014).[29] The protocol should be agreed between the sponsor and TGA.

This should be complemented by enhanced passive surveillance such that the proportion of vaccinated individuals with reported adverse events can be estimated (that is, where denominator data are available). While an indication for children <5 years is not currently being sought, safety data in this age group in ongoing studies should be made available when complete.

The Delegate also requested:

- *The expanded details (or a copy of the protocol) for the planned post-marketing surveillance in US NH 2017-2018 and 2018-2019 seasons.*
- *The expanded details (or the draft protocol) for the planned active post-marketing safety surveillance of the paediatric population from the 2019 season in Australia.*
- *The report of post-authorisation safety study (PASS) in EU NH 2015-2016, the report of enhanced passive safety surveillance (EPSS) in EU NH 2016-2017, and the study protocol for the 2017-18 season for Enzira?*
- *The basis for stating:*

  'Seqirus believes that the active surveillance as planned at the launch in 2019 will provide sufficiently robust post-marketing information in the paediatric population of 5 to 17 years.'

Other advice to the delegate

The Delegate's attention is drawn to the following amendments to the draft PI that were made by the sponsor, in response to RMP recommendations:

- Dosage advice has been formatted in a table.
- Contraindication for individuals with hypersensitivity to egg was removed, to align with the Immunisation Handbook.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available

[28] EMA/PRAC/222346/2014: Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU.
[29] EMA/PRAC/222346/2014: Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU.

version of the RMP document, the agreed changes become part of the risk management system.

The sponsor should update the pharmacovigilance plan as advised by ACV.

The suggested wording is:

> *Implement Afluria Quad EU-RMP version 5.0, 19 July 2017; DLP 31 May 2017 with ASA version 5.0, 22 June 2017 and any future updates as a condition of registration.*

The sponsor must update the pharmacovigilance plan to include conduct of enhanced active post-market safety surveillance for fever and other AESI[30] over additional seasons and between different vaccine batches.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Afluria Quad containing influenza virus haemagglutinin to extend the indications for use in 5-17 year olds. The full indications are now:

> *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 5 years and over.*
>
> *For full details regarding recommendations for influenza vaccination, please refer to the relevant national immunisation guidelines.*

Specific conditions of registration applying to these goods

- Implement Afluria Quad EU-RMP version 5.0, 19 July 2017; DLP 31 May 2017 with ASA version 5.2, 23 Jan 2018 and any future updates.
- Batch Release Testing and Compliance with the Certified Product Details

  It is a condition of registration that:

  – The first three batches of final bulk vaccine for each seasonal product be tested in the NF-κB Activation Assay, and that the assay be adapted to perform the testing under standard conditions and with at least one further dilution at a 4 fold increase in minimum concentration.

  – That the lipid content for each strain be calculated (in µg/ml) for each batch of final bulk vaccine and that limits be applied to each type/subtype based on the lipid content levels determined for clinical trial lots.

  – In addition to the above conditions of registration, it is also a condition of registration that all independent batches of Afluria Quad are not released for sale until samples and the manufacturer's release data have been assessed and you have received notification acknowledging release from the Laboratories Branch, TGA.

  For each independent batch of the product for release in Australia, the sponsor must supply the following:

  – A completed Request for Release Form;

  – Complete summary protocol for manufacture and QC;

  – At least 40 doses of each final batch of finished drug product with the Australian approved labels, PI and packaging;

[30] EMA/PRAC/222346/2014: Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU.

- Any other samples, reagents, reference material and standards required to undertake testing, as requested by Laboratories Branch, TGA.

Distribution of each batch of vaccine is conditional upon fulfilment of these conditions and receipt of a letter from the Laboratories Branch acknowledging release.

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

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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