



Australian Government  
Department of Health  
Therapeutic Goods Administration

# Australian Public Assessment Report for Influenza virus haemagglutinin

Proprietary Product Name: Flud Quad

Sponsor: Seqirus Pty Ltd (Australia)

**November 2019**

## 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.

### Copyright

© Commonwealth of Australia 2019

This work is copyright. You may reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the *Copyright Act 1968* or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given specific written permission from the Commonwealth to do so. Requests and inquiries concerning reproduction and rights are to be sent to the TGA Copyright Officer, Therapeutic Goods Administration, PO Box 100, Woden ACT 2606 or emailed to <[tga.copyright@tga.gov.au](mailto:tga.copyright@tga.gov.au)>.

# Contents

<b>Common abbreviations</b>	<b>4</b>
<b>I. Introduction to product submission</b>	<b>6</b>
Submission details	6
Product background	6
Regulatory status	7
Product Information	7
<b>II. Registration timeline</b>	<b>7</b>
<b>III. Submission overview and risk/benefit assessment</b>	<b>8</b>
Quality	8
Nonclinical	9
Clinical	10
Risk management plan	16
Risk-benefit analysis	18
Outcome	22
<b>Attachment 1. Product Information</b>	<b>23</b>

## Common abbreviations

Abbreviation	Meaning
ACV	Advisory Committee on Vaccines
AE	Adverse event
AESI	Adverse event of special interest
AICV	Australian Influenza Vaccine Committee
aQIV	Adjuvanted quadrivalent influenza vaccine
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Specific Annex
aTIV	Adjuvanted trivalent influenza vaccine
CBER	Center for Biological Evaluation and Research (USA)
CHMP	Committee for Medicinal Products for Human Use (EU)
CI	Confidence interval
CMI	Consumer Medicine Information
DRIVE	Development of Robust and Innovative Vaccine Effectiveness project
EMA	European Medicines Agency (EU)
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration (USA)
GMT	Geometric mean titre
GMR	Geometric mean titre ratio
HA	Haemagglutinin
HI	Haemagglutination inhibition
ILI	Influenza like illness
IM	Intramuscular
LL	Lower limit

Abbreviation	Meaning
MF59	MF59 adjuvant
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
NOCD	New onset of chronic disease
PCR	Polymerase chain reaction
PPS	Per protocol set
PSUR	Periodic Safety Update Report
RMP	Risk management plan
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SCR	Seroconversion rate
SH	Southern Hemisphere
SmPC	Summary of Product Characteristics (UK/EU)
TIV	Trivalent influenza vaccine
UK	United Kingdom
US(A)	United States (of America)
WHO	World Health Organization

## I. Introduction to product submission

### Submission details

<i>Type of submission:</i>	New chemical entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	24 September 2019
<i>Date of entry onto ARTG:</i>	1 October 2019
<i>ARTG numbers:</i>	316323, 313724
<i>, Black Triangle Scheme</i>	No
<i>Active ingredient:</i>	Influenza virus haemagglutinin
<i>Product name:</i>	Fluad® Quad inactivated quadrivalent influenza vaccine (surface antigen) adjuvanted
<i>Sponsor's name and address:</i>	Seqirus Pty Ltd (Australia) 63 Poplar Rd, Parkville VIC 3052
<i>Dose form:</i>	Injection, suspension
<i>Strength:</i>	60 µg haemagglutinin (HA)/0.5 mL
<i>Containers:</i>	Pre-filled syringe (needle-free) and pre-filled syringe (with attached needle)
<i>Pack sizes:</i>	1 and 10
<i>Approved therapeutic use:</i>	<i>Active immunisation against influenza in persons 65 years of age and older.</i>
<i>Route of administration:</i>	Intramuscular (IM)
<i>Dosage:</i>	A single 0.5 mL dose should be administered by intramuscular injection, preferably into the deltoid muscle of the upper arm.  Annual revaccination is recommended because immunity declines during the year after vaccination and circulating strains of influenza virus change from year to year.  For further information refer to the Product Information (PI).

### Product background

This AusPAR describes the application by the sponsor, Seqirus Pty Ltd (Australia), to register an adjuvanted inactivated quadrivalent influenza vaccine (aQIV) as Fluad Quad for active immunisation with the following indication:

*Active immunisation against influenza in persons 65 years of age and older.*

The sponsor has proposed the following dosing and administration instructions:

*A single 0.5 mL dose should be administered by intramuscular injection, preferably into the deltoid muscle of the upper arm.*

*Annual revaccination is recommended because immunity declines during the year after vaccination and circulating strains of influenza virus change from year to year.*

Each dose (0.5 mL) of Flud Quad contains 15 µg haemagglutinin (HA) of each four strains (2 x 'A' strains; 2 x 'B' strains) of influenza virus antigen as well as the adjuvant MF59. The four influenza strains for the Southern Hemisphere influenza season will be selected according to the recommendations of the World Health Organization (WHO) and the Australian Influenza Vaccine Committee. (AICV) for the season.

Flud Quad has been shown to evoke antibody responses to the viral surface glycoproteins HA and neuraminidase. These antibodies provide protection against clinical illness in a high proportion of vaccine recipients. The antibody response to Flud Quad is similar to Flud, the latter being the adjuvanted trivalent influenza vaccine (aTIV) from the same sponsor. The difference between the two vaccines is the addition of a B strain from the alternate lineage to Flud Quad.

The Flud Quad adjuvant MF59 broadens the overall immune response allowing the vaccine to offer greater protection against heterologous strains of the virus. This may be important when there is a mismatch between the virus strains included in the vaccine and the strains circulating in the community. The antibody response is increased when compared to the response to non adjuvanted inactivated influenza vaccine. This increased response is seen particularly in elderly subjects (subjects 65 years of age and older) with low pre-immunisation titres and/or with underlying diseases (diabetes, cardiovascular and respiratory diseases) who are at increased risk of complications of influenza infection.

Flud Quad is produced using the same manufacturing platform as the licensed Flud. The dose and concentration of MF59 and HA per strain used in Flud Quad are also similar to Flud.

## **Regulatory status**

This is an application to register a new chemical entity for Australian regulatory purposes. Flud, the adjuvanted trivalent influenza vaccine (aTIV) from the same sponsor, was registered in Australia on 15 October 2002.

The aTIV is currently licensed for use in individuals ≥ 65 years of age in 29 countries worldwide, and for use in individuals 6 months to <2 years of age in Canada.

## **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.

**Table 1: Timeline for Submission PM-2019-00120-1-2**

Description	Date
Submission dossier accepted and first round evaluation commenced	1 March 2019
Evaluation completed	29 July 2019
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	31 July 2019
Sponsor's pre-Advisory Committee response	6 August 2019
Advisory Committee meeting	20 August 2019
Registration decision (Outcome)	24 September 2019
Completion of administrative activities and registration on ARTG	1 October 2019
Number of working days from submission dossier acceptance to registration decision*	123

\*Target timeframe for priority applications is 150 working days from acceptance for evaluation to the decision.

### III. Submission overview and risk/benefit assessment

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

#### Quality

There are no issues from the quality evaluation that would indicate the product should not be registered.

There are however items that need to be provided before it is possible to provide assurances that the product is able to meet all of the requirements of the Therapeutics Goods Act 1989 and its associated instruments. Quality conditions have been proposed to ensure the product is fully compliant with all of the previously mentioned instruments before release into the market and these include the following items.

#### ***Batch release testing and compliance with the Certified Product Details***

It is a condition of registration that all independent batches of Flud Quad imported into Australia 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 imported into Australia, the sponsor must supply the following:

- A completed Request for Release Form, available from [vaccines@health.gov.au](mailto:vaccines@health.gov.au).



- Complete summary protocols for manufacture and quality control, including all steps in production.
- At least 20 (twenty) doses of the first consignment of each batch of Flud Quad with the Australian approved labels, PI and packaging.
- At least 10 (ten) doses of any further consignment of each batch of Flud Quad with the Australian approved labels, PI and packaging and at least 20 (twenty) doses of any further consignment of each batch of Flud Quad with the Australian approved labels, PI and packaging.
- Certificate of Release from a regulatory agency acting for the country of origin such as an official medicines control laboratory (OMCL) (if available).
- Any reagents, reference material and standards required to undertake testing, as requested by Laboratories Branch, TGA.

Distribution of each shipment 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 Biomedicines and Influenza Vaccines Section, Laboratories Branch before release of each batch and with sufficient lead time to allow for Laboratories Branch testing. The address for courier delivery is:

Influenza Unit, Biomedicines and Influenza Vaccines Section  
Laboratories Branch, Therapeutic Goods Administration  
136 Narrabundah Lane, Symonston, ACT 2609.

All shipments (including reagents) must be sent to TGA from the Australian sponsor/agent who will be required to facilitate the import and customs clearance process.

### ***Certified Product Details***

An electronic copy of the Certified Product Details (CPD) as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) <https://www.tga.gov.au/guidance-7-certified-product-details> should be provided upon registration of the therapeutic good. In addition, an updated CPD, for the above products incorporating the approved changes is to be provided within one month of the date of approval letter. A template for preparation of CPD for biological prescription medicines and Vaccines can be obtained from the TGA website <https://www.tga.gov.au/form/certified-product-details-cpd-biological-prescription-medicines>. The CPD should be sent as a single bookmarked PDF document to [vaccines@health.gov.au](mailto:vaccines@health.gov.au) as soon as possible after registration/approval of the product or any subsequent changes as indicated above.

## **Nonclinical**

The evaluator states that only two new non-clinical studies were submitted: one immunogenicity study in mice with a quadrivalent vaccine (containing the adjuvant, MF59) and one fertility, embryofetal and early postnatal development study in rabbits with the trivalent vaccine Flud. The non-clinical evaluator provided the following recommendations to the Delegate:

- Immunogenicity of the aQIV was demonstrated in mice, although the quadrivalent formulation was less immunogenic than monovalent formulations of individual influenza strains.

- Previously evaluated repeat-dose toxicity studies with an aTIV at total HA doses higher than the clinical dose showed only slight local reactions and slight systemic effects of a transient response to the adjuvant or an immune response to the vaccine antigens.
- No effects on female fertility, embryofetal and early postnatal development with aTIV Fluad were observed in rabbits.
- There are no nonclinical objections to registration of Fluad Quad vaccine for the active immunisation against influenza in persons 65 years of age and older.
- Amendments to the draft PI were recommended but these are beyond the scope of this AusPAR.

## Clinical

The clinical data to support the registration of aQIV is primarily based on the results of the pivotal aQIV immunogenicity and safety study (Study V118\_20). A number of aTIV studies were also submitted as supportive evidence as follows:

- One new key supportive aTIV study: Study V70\_27
- A number of aTIV studies (most previously evaluated by the TGA):
  - Studies V7P3, V7P5, V7P7, V7P8, V7P25, V7P31, V7P34, V7P35, V63P1, V70P1 and V104P3
  - Revaccination studies: Studies V7P3X1, V7P3X2, V7P5X1, V7P5X2, V7P7X1, V7P8X1 and V7P25X1
  - Two aTIV effectiveness studies: Studies C70P1 and V70\_490BTP
  - Studies V104P3 and V7P38 were two dose-ranging studies. These studies evaluated the effect of various antigen and MF59 dose levels on immune response to aTIV.

The choice of the current aQIV formulation is supported by these studies. Dose for the second B antigen was same as previously approved dose of B antigen in aTIV.

## Efficacy/immunogenicity

### *Pivotal Study V118\_20*

This is a Phase III, randomised, double blind, controlled, multicentre study. The study evaluated the safety and immunogenicity of a MF59 adjuvanted quadrivalent influenza vaccine (aQIV), in comparison with an MF59 adjuvanted trivalent influenza vaccine (aTIV) and an MF59 adjuvanted TIV containing the alternate B strain, in adults aged 65 years and above. The co-primary immunogenicity objectives were:

- to demonstrate that vaccination with aQIV elicits an immune response that is not inferior to that of an aTIV containing the same virus strains as the licensed adjuvanted TIV (FLUAD, aTIV-1), and an aTIV containing the alternate B strain (aTIV-2) among adults 65 years of age; and
- to assess the immunogenicity of aQIV in adults  $\geq 65$  years of age based on the CBER (Center for Biologics Evaluation and Research) criteria.

Overall, a total of 1778 subjects enrolled in the study and 1776 subjects (99.9%) received vaccination. Five subjects were early terminated prior to Day 22 and one subject from aQIV group did not provide evaluable blood sample at Day 22. These 6 subjects were excluded from the full analysis set (FAS) immunogenicity set. In total, 1770 subjects were

included in the FAS. The median overall age of subjects was 71 years; the minimum age was 65 years, and the maximum was 90 to 97 years. A majority of subjects (56.6%) were female versus 43.4% male.

Analysis of immunogenicity was performed on the per protocol set (PPS) Immunogenicity (primary analysis) and on the FAS immunogenicity set. The primary analysis of immunological superiority for the B strains (secondary objective 2) was based on the FAS with supportive analysis performed on the PPS.

#### *Primary objective*

First co-primary immunogenicity objective

The immunogenicity results in the PPS are presented in the table below.

**Table 2: Immunological non-inferiority of aQIV versus aTIV comparators against homologous strains (per protocol set)**

Strain	aQIV N = 872	aTIV-1 N = 436	aTIV-2 N = 433	95% CI
	GMT	GMT	GMT	GMT Ratio
A/H1N1	65.01		75.16	1.16 (1.05, 1.27)
A/H3N2	294.91		293.31	0.99 (0.90, 1.09)
B/Yamagata	24.67	N/A	24.30	0.99 (0.90, 1.08)
B/Victoria	30.78	30.13	N/A	0.98 (0.89, 1.08)
	SCR	SCR	SCR	SCR Differences
A/H1N1	35.21		38.43	3.23 (-1.30, 7.76)
A/H3N2	39.33		39.70	0.37 (-4.23, 4.96)
B/Yamagata	16.4	N/A	15.47	-0.93 (-5.13, 3.27)
B/Victoria	13.42	12.16	N/A	-1.26 (-5.07, 2.55)

*GMT*: The pre-specified non-inferiority criteria for the adjusted geometric mean titre (GMT) on Day 22 were met for all 4 homologous strains. The upper bounds of the two-sided 95% confidence interval (CI) for the GMT ratios (aTIV/aQIV) for all homologous strains did not exceed the non-inferiority margin of 1.5. The results for the FAS were comparable to the PPS.

*SCR*: The pre-specified non-inferiority criteria for the difference in seroconversion rate (SCR) between aTIV and aQIV were met for all 4 homologous strains. The upper bounds of the 95% CI of the intergroup difference for SCR (aTIV minus aQIV) did not exceed the non-inferiority margin of 10% for all 4 strains. The results for the FAS were comparable to the PPS.

#### *Second co-primary immunogenicity objective (according to CBER<sup>1</sup> Criteria)*

The lower limit of the two-sided 95% CI for the proportion of subjects achieving a post-vaccination HI titre<sup>2</sup>  $\geq 1:40$  for A/H1N1 and A/H3N2 strains were above 60%, but were below 60% for both B strains; therefore, the CBER success criteria for proportion of subjects with HI titre  $\geq 1:40$  were met for A strains, but not for B strains. The proportion of subjects with HI titre  $\geq 1:40$  against B strains in the aTIV-1 and aTIV-2 groups were similar to those obtained for aQIV (lower limits of the 95% CI were below 60%). Results for the FAS were comparable to the PPS.

<sup>1</sup> The Center for Biologics Evaluation and Research, US Food and Drug Administration; Maryland, USA.

<sup>2</sup> The highest dilution of serum that prevents haemagglutination is called the HI titre.

The lower limit of the two-sided 95% CI for the proportion of subjects achieving SCR for HI antibody for A/H1N1 and A/H3N2 strains were above 30%, but were below 30% for both B strains (B/Yamagata and B/Victoria). Therefore, the CBER success criteria for SCR were met for A strains, but not for B strains. SCR rates for B strains in the aTIV-1 and aTIV-2 groups were similar to those obtained for aQIV (lower limits of the 95% CI were below 30%). Results for the FAS were comparable to the PPS.

#### *Secondary objectives*

The secondary objective for immunological superiority (SCR difference and GMT ratio) of aQIV compared to aTIV-1 and aTIV-2 for the alternate B strain was met.

Additional secondary immunogenicity endpoints including the percentage of subjects with a HI titre  $\geq 1:40$ , SCRs, and GMRs were analysed. Overall across all endpoints, immunogenicity results were similar between aQIV and aTIV vaccines for A strains and respective B strains.

The subgroup analyses confirmed similar immunogenicity of aQIV and aTIV in subjects of different age groups ( $\geq 65$  to  $74$ ,  $\geq 75$  to  $84$ , and  $\geq 85$  years), gender, race, comorbidity status and previous influenza vaccination history.

#### ***Study V70\_27 Key supportive aTIV study***

Study V70\_27 has not been submitted to TGA previously. It is noted that this study had been evaluated by the FDA at the time when aTIV (Fluad) was assessed for licensure in the US.

Study V70\_27 is a Phase III, randomised, controlled, observer blind, multicentre study. The study evaluated the lot consistency (3 aTIV lots) and also the immunogenicity, safety of aTIV in comparison to non adjuvanted vaccine (Agrimflu). The trial was performed between 2010 and 2011. The study was conducted in 7109 subjects  $\geq 65$  years of age who were healthy or had comorbidities that increased their risk of complications from influenza infection. Subjects were stratified into 2 age cohorts (65 to 75 years and  $> 75$  years), and were randomised within each age cohort in a 1:1:1:3 ratio to receive 1 of the 3 consecutive lots of aTIV or a single lot of a non adjuvanted TIV (Agrimflu), respectively. Importantly, all 4 vaccine products contained the identical antigens for the 3 influenza strains. All subjects were followed for approximately one year after vaccination.

#### *Co-primary objectives*

The study had 3 co-primary objectives that were evaluated in a stepwise fashion. The first co-primary objective of lot to lot consistency of the 3 aTIV lots was met. The second co-primary objective of immunological non-inferiority relative to Agriflu was met against all homologous strains, but the overall pre-specified superiority criteria for GMT ratio (lower limit (LL) of the 95% CI  $> 1.5$ ) and SCR difference (LL of the 95% CI  $> 10\%$ ) were not met for all homologous strains. The superiority threshold was achieved only for SCR differences against the A/H3N2 strain. The third co-primary objective of immunogenicity of aTIV according to the CHMP criteria;<sup>3</sup> current at that time was met and at Day 22, the aTIV group met all 3 of the CHMP criteria for each strain against both homologous and heterologous strains.

The *post hoc* analyses demonstrated that aTIV elicited significantly higher SCRs (LL of the 95% CI exceeded 0) and GMT levels (LL of the 95% CI exceeded 1) than TIV against all 3 homologous strains, including after multiplicity adjustment.

<sup>3</sup> CPMP/BWP/214/96 Note for guidance on harmonization of requirements for influenza vaccines. This Note for Guidance and its Annex have been withdrawn as their content was considered outdated with respect to current understanding of critical elements of the annual strain update (see EMA/CHMP/VWP/232674/2013).

### *Secondary objectives*

The first of the secondary objectives was to evaluate immunological non-inferiority and superiority of aTIV versus TIV for homologous strains in high-risk subjects with predefined comorbidities. Non-inferiority was demonstrated first, followed by assessment of superiority. None of the strains met the criterion for superiority.

The second of the secondary objectives was to evaluate immunological non-inferiority and superiority of aTIV versus TIV for heterologous strains in all subjects and in high risk subjects. The aTIV was shown to be non-inferior to TIV against the 3 heterologous strains in all subjects or among the high risk subgroup but the superiority criteria against the 3 heterologous strains were not reached for the overall study population or among the high risk subgroup.

Clinical efficacy against influenza like illness (ILI), not microbiologically confirmed, was evaluated as another secondary endpoint. There was no significant difference among the overall study population or among the high risk subgroup in the clinical effectiveness observed between the aTIV and the TIV groups in terms of the incidence of ILI, exacerbation of pre-existing chronic conditions, healthcare utilisation or mortality in the 12 month follow-up period.

### ***Supportive Flud (aTIV) studies***

Most of the supportive aTIV studies were evaluated by the TGA at the time of Flud registration assessment and are not discussed in detail here. Overall the results from supportive aTIV studies were generally consistent with what has been observed in Study V70\_27. The immune response to aTIV is increased when compared to the response after vaccination with non adjuvanted TIV and is most pronounced for B and A/H3N2 influenza antigens. A similar immunogenicity profile has been noted after a second and third immunisation with aTIV. Increased antibody rises after immunisation with aTIV have also been shown against heterovariant strains, antigenically different from those included in the vaccine.

### ***Flud (aTIV) studies assessing clinical effectiveness***

The sponsor has provided two published non-interventional studies:

- Study C70P1; and
- Study V70\_49OBTP.

In these two studies, the effectiveness of aTIV has been assessed and compared to non adjuvanted TIV. It is noted that these two studies had been submitted to the Medicines and Healthcare products Regulatory Agency (MRHA) and the brief summary of these two studies have been included in the United Kingdom (UK) Summary of Product Characteristics (SmPC) for Flud. Brief summaries of the two studies are presented below.

#### ***Study C70P1***

This was a non-interventional prospective cohort study. This study was conducted in the 5 Northern Italian health districts during the 2006/2007, 2007/2008 and 2008/2009 influenza seasons.<sup>4</sup> The study assessed the relative risk of hospitalisations due to influenza or pneumonia during the influenza season amongst subjects  $\geq 65$  years of age who received either aTIV (Flud) or non adjuvanted TIV (Agrippal). Study outcomes were identified through the automated administrative, multipurpose databases of the Italian National Healthcare System. The study outcome was defined as a hospital discharge

---

<sup>4</sup> Mannino S, Villa M, Apolone G, Weiss NS, Groth N, Aquino I, Boldori L, Caramaschi F, Gattinoni A, Malchiodi G, Rothman KJ. (2012). Effectiveness of adjuvanted influenza vaccination in elderly subjects in northern Italy. *Am J Epidemiol.* 2012 Sep 15;176(6):527-33. Epub 2012 Aug 31.

diagnoses for influenza or pneumonia at least 3 weeks following vaccination during defined periods of the influenza season based on the epidemic curves of the national influenza surveillance.

Over the 3 influenza seasons, the study enrolled 107,661 subjects of  $\geq 65$  years of age, with 43,667 subjects participating for more than 1 year. Overall, 170,988 vaccinations were administered comprising of 88,449 doses of aTIV and 82,539 doses of TIV. The primary analysis (primary endpoint of hospitalisation due to influenza or pneumonia) was based on outcomes occurring during and including adjacent weeks to the peak of the influenza season. Laboratory confirmation of influenza was not available.

Due to local immunization policy, subjects who received aTIV had worse baseline health status than those subjects who received TIV. After adjusting for confounding variables (baseline health status, others), the risk of hospitalisation for influenza or pneumonia was 25% lower for aTIV recipients relative to TIV recipients (relative risk = 0.75, 95% CI: 0.57 to 0.98). Outside of the influenza season, the baseline risk of hospitalisation was higher for aTIV than for TIV recipients indicating that the analysis had not removed all confounding.

#### *Study V70\_490BTP*

This was a small retrospective case-control study conducted in 2011/2012 season. The study used a test-negative design to estimate vaccine effectiveness of aTIV versus a non adjuvanted TIV (predominantly Fluviral), or no vaccination in subjects  $\geq 65$  years of age in 3 Canadian Health Authorities.<sup>5</sup> Cases were defined as reverse transcription polymerase chain reaction (RT-PCR) confirmed influenza following onset of ILI and controls were defined as patients with ILI but who were influenza PCR-negative.

In total, 282 subjects (84 cases and 198 controls) were enrolled among whom 227 subjects had received routine vaccination, comprising of 165 subjects vaccinated with aTIV; 62 with a non adjuvanted TIV and 55 non-vaccinated subjects. The majority of the participants reported at least a one chronic disease (89%). After adjustment for confounding variables (age, sex, residency in long-term care facility, chronic conditions, region and week of testing), the absolute vaccine effectiveness for aTIV was 58% (95% CI: 5%, 82%;  $P < 0.04$ ) whereas the non adjuvanted TIV was ineffective compared to no vaccination. The relative vaccine effectiveness for aTIV to non adjuvanted TIV was 63% (95% CI: 4%, 86%;  $P = 0.04$ ). The limitation of this study include single season with low influenza activity and very small sample size.

## **Safety**

The clinical safety database to support the licensure of aQIV in individuals  $\geq 65$  years of age includes 888 subjects exposed to aQIV and 5146 subjects exposed to aTIV (aTIV-1) or aTIV-2.

In Study V118\_20, the reactogenicity profiles of the aQIV and aTIV vaccines were generally comparable. The observed rates of solicited local adverse events (AE) were slightly higher in the aQIV group compared to the aTIV groups (aTIV-1 and aTIV-2). The majority of local reactions were of mild or moderate severity and resolved within 3 days.

The most commonly reported local solicited AE was injection site pain. Severe pain was reported by  $< 1\%$  subjects in each study group. The observed rates of solicited systemic AEs were also similar between the vaccine groups. The most commonly reported systemic solicited AEs were fatigue ( $< 17\%$  of subjects), headache ( $< 13\%$ ), and arthralgia ( $< 10\%$ ). Severe systemic solicited AEs were uncommon in all vaccine groups and varied from 0%

<sup>5</sup> Van Buynder PG1, Konrad S, Van Buynder JL, Brodtkin E, Krajden M, Ramler G, Bigham M. (2013). Vaccine The comparative effectiveness of adjuvanted and unadjuvanted trivalent inactivated influenza vaccine (TIV) in the elderly.. 31(51):6122-8. doi: 10.1016/j.vaccine.2013.07.059. Epub 2013 Aug 6.



to 1.4% in study groups. Most solicited reactions were reported as mild or moderate in intensity and resolved within 3 days. The percentages of subjects reporting unsolicited AEs, including those assessed as possibly related to vaccination were comparable across study groups. No unsolicited AEs led to subject withdrawal from the study in any vaccine group.

No treatment related serious adverse events (SAE) or deaths were reported in the study. Two adverse events of special interest (AESI) were reported during the study: one in the Flud group, and one in the Flud Quad group. Neither of the AESIs was considered to be related to study vaccine. The frequency of unsolicited events leading to new onset chronic disease (NOCd) was similar across study groups: Flud Quad (2.6%); Flud (3.6%) and aTIV-2 (3.2%). NOCDs were heterogeneous in nature and consistent with the clinical conditions spontaneously occurring in subjects 65 years of age and older. No reported NOCDs were considered related to study vaccine.

In Study V70\_27, the reactogenicity profiles of aTIV and TIV vaccines were generally comparable. The observed rates of solicited local AEs were higher in the aTIV group compared to the TIV group. The majority of local reactions were of mild or moderate severity, and of short duration. The most commonly reported local solicited AE was injection site pain. Severe pain was reported by <1% subjects in each study group. The observed rates of solicited systemic AEs were also slightly higher in the aTIV group compared to the TIV group (32% versus 26%). The most commonly reported systemic solicited AE was myalgia (15% aTIV versus 10% TIV). Severe systemic solicited AEs were uncommon (<1%) in both vaccine groups. Seven systemic AEs requiring emergency room visit or hospitalisation were reported by 5 subjects (2 subjects in the aTIV group versus 3 subjects in the TIV group). Of the 5 subjects, 4 subjects were either lost to follow up or withdrew consent, and for 1 subject the reactions subsided by Day 6. Overall, this key supportive aTIV study showed that except for a mild increase in reactogenicity, the safety profile of aTIV was similar to TIV. An increase in reactogenicity is expected with adjuvanted vaccines.

Overall, the nature and frequency of solicited AEs for aQIV in subjects  $\geq 65$  years of age were similar to the licensed aTIV with a slight increase in reactogenicity. No safety concerns were observed from the aQIV and aTIV studies including assessment of SAEs with an outcome of death, SAEs, NOCDs and AESIs.

### ***Post-market safety data for aTIV***

Since aQIV is not currently licensed in any country, there is no post-marketing safety data. The post-marketing safety data of aTIV is submitted instead.<sup>6</sup> The post-marketing safety assessment of aTIV spans over 20 years. Since the initial licensure of aTIV in Italy in 1997, over 102 million doses of seasonal aTIV vaccine have been distributed worldwide, mostly for use in older adults. The cumulative reporting period for the analysis was from 1 May 1997 to 15 March 2018; and was based on the aTIV Periodic Safety Update Report (PSUR) No. 41. During this period, over 102 million doses of aTIV were distributed, and 2241 spontaneous aTIV confirmed individual case safety reports were received.

The analysis of the cumulative post-marketing safety data for aTIV showed that the safety profile of aTIV is consistent with the safety profile in the clinical studies of aTIV and aQIV presented in this application. No new safety concerns have been identified in the aTIV post-marketing safety assessment.

<sup>6</sup> The post-marketing experience with aTIV may be relevant to aQIV because both vaccines are manufactured using the same process and have overlapping compositions (PI Section 4.8).

## Risk management plan

The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 3.<sup>7</sup>

**Table 3: Ongoing safety concerns**

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine (R)	Additional (A)	R	A
<b>Important identified risks</b>	Nil	–	–	–	–
<b>Important potential risks</b>	Convulsion	Ü*	–	Ü	–
	Neuritis	Ü*	–	Ü	–
	Encephalitis	Ü*	–	Ü	–
	Vasculitis	Ü*	–	Ü	–
	Guillain-Barre Syndrome (GBS)	Ü*	–	Ü	–
	Demyelination	Ü*	–	–	–
	Bell's palsy	Ü*	–	–	–
	Immune Thrombocytopaenic Purpura (ITP)	Ü*	–	Ü	–
<b>Missing information</b>	Safety in immunocompromised individuals	Ü*	–	Ü	–

\* Enhanced Passive Safety Surveillance for influenza vaccines

In the submitted risk management plan (RMP), the sponsor mentioned the Development of Robust and Innovative Vaccine Effectiveness (DRIVE) project, which is an Innovative Medicines Initiative (IMI) project. DRIVE was launched in July 2017 to address the regulatory recommendation to perform post-authorisation effectiveness studies as per the Guideline on Influenza Vaccines.<sup>8</sup> GSK, Sanofi Pasteur, Abbott and Seqirus contributed to

<sup>7</sup> 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.

<sup>8</sup> EMA/CHMP/VWP/457259/2014



the genesis of this project, originally referred to as Joint Influenza Vaccine Effectiveness studies (JIVES). The DRIVE project is a unique public private partnership involving, in addition to manufacturers, academia and public health institutes.<sup>9</sup> Vaccine effectiveness estimates will be considered within the context of the multitude of factors aside from the vaccine that could determine the effectiveness of the vaccine as well as with consideration for the applied study design. Seqirus will not be the study sponsor or owner of the data. Timelines are driven by the overall project and timelines of the existing surveillances. Over its lifetime, the project is expected to progressively expand the existing infrastructure to enhance the opportunities for Seqirus to document vaccine effectiveness of aQIV post-marketing. The study timelines and associated period of the data collection depend on the availability of the influenza vaccines, start of the vaccination programme and start of the influenza virus circulation which will vary by study location and season. The report is expected to be available for submission in December following the initial season of aQIV launch and annually thereafter. It is also confirmed that, if registered and supplied, the safety of the vaccine will be monitored in the AusVaxSafety surveillance program.<sup>10,11</sup>

The RMP evaluator has proposed the following Conditions of Registration:

Any changes to which the sponsor has agreed should be included in a revised RMP and Australian Specific Annex (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:

*The Fluad Quad EU-Risk Management Plan (RMP) (version 1.0, dated 9 January 2019, data lock point 31 October 2018), with Australian Specific Annex (version 1.0, dated 17 January 2019), included with submission PM-2019-00120-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*

The following wording is recommended for the PSUR requirement:

*An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).*

*Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.*

*The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the*

<sup>9</sup> Sponsor comment: This project is considered key in relation to the regulatory recommendation to perform post-authorisation effectiveness studies as per the European Medicines Agency (EMA) guidance.

<sup>10</sup> AusVaxSafety surveillance is a collaborative initiative led by the National Centre for Immunisation, Research and Surveillance (NCIRS) and involves vaccine safety experts, state and territory public health systems, general practitioners and children's hospitals across Australia. It is funded by the Australian Government Department of Health.

<sup>11</sup> Sponsor clarification: If registered and listed in the National Immunization Program (NIP), the reactogenicity of the vaccine will be monitored in the AusVaxSafety surveillance program.

registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

## Risk-benefit analysis

### Delegate's considerations

The submitted single pivotal study assessed the safety and immunogenicity of aQIV. The study demonstrated that aQIV was non-inferior to aTIV comparators in terms of antibody response to the three vaccine strains. The aQIV was also demonstrated to be immunologically superior to aTIV-1 (Fluad) and aTIV-2 for the B strain that was not included in each aTIV vaccine. However, the immune responses against the B strains were low for both the aQIV and the two aTIV comparators, so the CBER criteria for absolute immune response were not met.

In response to the TGA's question regarding the low response to the B strains, the sponsor provided the analysis from their 16 clinical trials conducted with adjuvanted TIV versus non adjuvanted TIV. These data show that while there is significant variability in immune responses against different B strains included in the vaccines, the addition of the MF59 adjuvant induces a higher immune response than the non adjuvanted TIV, and in general, aTIV elicited acceptable immune response against the B strain over multiple seasons (against the CBER criteria). Specifically, Fluad met the CBER criterion for SCR in 13 of the 16 studies and met the CBER criterion for percentage of subjects with post-vaccination HI  $\geq 1:40$  in 15 of the 16 studies (see the Table 4 below).

**Table 4: B strains/CBER criteria for licensure in 16 aTIV/TIV studies at post vaccination (Day 21 to 29) (FAS)**

Study	N	aTIV Lower bound of 2-sided 95% CI for B strain		N	TIV Lower bound of 2-sided 95% CI for B strain	
		SCR <sup>a</sup>	$\geq 1:40^b$		SCR <sup>a</sup>	$\geq 1:40^b$
V7P3	46	71.1	82.1	46	41.1	61.2
V7P5	202	38.1	84.0	100	16.9	57.9
V7P6	47	55.1	66.7	95	40.1	53.7
V7P7	106	66.2	78.8	99	59.6	70.5
V7P8	192	30.1	79.0	99	22.4	69.4
V7P17	150	40.4	96.3	154	20.4	96.4
V7P24	149	28.5	91.4	147	14.2	79.8
V7P25	137	55.6	97.3	134	42.7	97.3
V7P26	71	56.9	94.9	70	54.9	94.9
V7P27	100	27.6	88.7	206	25.3	90.0
V7P30	301	41.4	95.3	150	29.6	92.4
V7P34	445	35.0	95.9	111	17.5	91.0
V7P35	209	22.7	95.9	119	14.1	92.8
M63P1	175	81.6	92.7	174	80.2	95.0
V70_27	3479	45.3	62.9	3482	39.8	57.3
V104P3	47	32.1	42.2	44	18.6	36.7
All	5856	46.5	75.5	5230	40.1	67.8
Highlighting	Meets CBER criteria		Does not meet CBER criteria			

a. SCR = percentage of subjects achieving seroconversion (CBER criterion = lower bound of 95% CI  $\geq 30\%$ )

b.  $\geq 40$  = percentage of subjects achieving postvaccination HI titer  $\geq 1:40$  (CBER criterion = lower bound of 95% CI  $\geq 60\%$ )

Given the variation observed in absolute measurements of immunogenicity (CBER criteria), the Delegate considers that the relative non-inferiority comparison of immunogenicity between aQIV and aTIV is acceptable for assessing the possible benefit of aQIV.

Overall, the immunogenicity results from the pivotal study have shown that the addition of a fourth strain to the formulation does not impact the immunogenicity of the other 3 strains included in the aQIV vaccine, and non-interference has been demonstrated.

Additional supportive data was provided from the immunogenicity and effectiveness studies conducted with aTIV. The key supportive aTIV study (Study V70\_27) demonstrated that MF59 adjuvanted TIV elicited higher immune responses as compared

to non adjuvanted TIV against homologous and heterologous strains in the general elderly population and in the subgroup of subjects who are at high risks for influenza complications. The two published aTIV effectiveness studies provided some evidence to support the benefit of MF59 adjuvanted TIV compared with non adjuvanted TIVs in reducing influenza related hospitalisation in the elderly population.

With regards to safety, the submitted data showed that the nature and frequency of solicited AEs for aQIV in subjects  $\geq 65$  years of age were similar to the licensed aTIV with a slight increase in reactogenicity, and there are no safety concerns observed from the aQIV and aTIV studies including assessment of SAEs with an outcome of death, SAEs, NOCDs and AESIs.

As stated by the clinical evaluator, the limitations of the aQIV data include single season data on immunogenicity, no data on people who are immunocompromised, no assessment on aQIV vaccine efficacy, and so on. The Delegate accepts that the immunogenicity outcomes may serve as surrogate for vaccine efficacy but there are uncertainties regarding the direct extrapolation of immunogenicity outcomes to vaccine efficacy. Nevertheless, based on the immunogenicity comparisons of aQIV versus aTIV, it is expected that aQIV should deliver similar efficacy to that of aTIV in terms of the protection against the three common influenza strains included in the vaccines and it is likely that aQIV may provide better protection than aTIV against the alternate B strains that is not included in aTIV.

In the submitted RMP, the sponsor mentioned their involvement with the European Union's (EU) DRIVE project. If aQIV is licenced and supplied in the EU, brand specific vaccine effectiveness data in the EU may become available from the DRIVE project. The sponsor should consider how the post-marketing vaccine effectiveness data for Flud Quad can be collected in Australia.<sup>12</sup>

The Delegate agrees with the clinical evaluator that there is a favourable benefit risks balance for the use of aQIV in people older than 65 years of age for active immunisation against influenza infection. The Delegate sought advice from TGA's Advisory Committee on Vaccines (ACV) (see below for further details).

### Summary of issues

The vaccine efficacy of Flud Quad (aQIV) has not been assessed. The submitted single pivotal study compared the safety and immunogenicity of Flud Quad to that of Flud (aTIV). The study demonstrated that aQIV was non-inferior to aTIV comparators (aTIV1 and aTIV2) in terms of immune responses to the three vaccine strains. The aQIV was also shown to be immunologically superior to aTIV-1 (Flud) and aTIV-2 for the B strain that was not included in each aTIV vaccine. However, the absolute immune responses against the B strains were low for both the aQIV and the two aTIV comparators, so the immunogenicity criteria according to CBER criteria were not met.

A number of aTIV studies were submitted as the supportive evidence. These include two observational effectiveness studies.

### Proposed action

The Delegate had no reason to say, at this time, that the application for Flud Quad should not be approved for registration.

The final decision will be made following the ACV advice and satisfactory discussion on the PI and the Conditions of Registration.

---

<sup>12</sup> Sponsor response: The vaccine effectiveness in the Australian setting will be addressed by routine pharmacovigilance activities. All reports of vaccination failure are collected and entered into the Seqirus safety database.

**Request for ACV advice**

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

1. In the pivotal study, the immune responses against the B strains were low for both the aQIV and the two aTIV comparator vaccines, and the CBER criteria for absolute immune responses were not met for the B strains. Does the ACV have any concerns about this result?
2. Vaccine Efficacy has not been assessed. Does the ACV support the registration of Flud Quad on the basis of the immunogenicity results from Study V118\_20 and the supportive immunogenicity and effectiveness data from aTIV studies?

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 the application.

**Advisory committee considerations**

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

The ACV, taking into account the submitted evidence of efficacy, safety and quality, considered the vaccine:

Flud Quad inactivated quadrivalent influenza vaccine (surface antigen), adjuvanted. Each 0.5 mL dose contains influenza virus surface antigens (haemagglutinin and neuraminidase) of each of four antigens representative of the influenza virus types expected to circulate in the Southern Hemisphere winter (specifically, 15 micrograms of influenza virus haemagglutinin from each of two A strains (A/H1N1 and A/H3N2) and two B strains (Yamagata lineage and Victoria lineage)); to have an overall positive benefit-risk profile for the indication:

*Active immunisation against influenza in persons 65 years of age and older.*

In providing this advice the ACV:

- was of the view that Flud Quad (aQIV) was non-inferior to Flud (aTIV) in terms of immunogenicity to the three vaccine strains that were common to both vaccines, as shown in the pivotal study.
- that lower immune response to the B strains with both the aQIV and aTIV in the pivotal study is likely due to seasonal variation, as the data from many previous aTIV studies showed a significant variability in immune responses against different B strains and there were good immune responses to the B strains in the majority of these studies.
- noted the vaccine efficacy for aQIV has not been assessed, and the ACV advised that this was acceptable. As per the TGA adopted EU guidance;<sup>13</sup> an influenza vaccine that has a manufacturing process similar to that of an authorised vaccine already evaluated may be evaluated based on comparative studies of safety and immunogenicity (rather than efficacy) in some population sub-groups.
- was of the view that the safety data were acceptable. The nature and frequency of solicited adverse events for the aQIV in subjects ≥ 65 years of age were similar to the licensed aTIV with a slight increase in reactogenicity.

---

<sup>13</sup>EMA/CHMP/VWP/457259/2014 Guideline on Influenza Vaccines Non-clinical and Clinical Module

- noted the single season data with aQIV, and the heavy reliance on the effectiveness, safety and immunogenicity data from experience with adjuvanted inactivated trivalent vaccines.
- noted the risk of inadvertent administration of the proposed vaccine to children and younger adults, and suggested risk minimisation activities (for example, colour coding) to differentiate influenza vaccines for use in different age groups.

### **Proposed PI/ CMI amendments**

The committee commented that it would be useful for the PI to provide information on inadvertent (off-label) use of the vaccine in paediatric patients [information redacted].

### **Specific advice**

The ACV advised the following in response to the Delegate's specific questions on the submission.

1. In the pivotal study, the immune responses against the B strains were low for both the aQIV and the two aTIV comparator vaccines, and the CBER criteria<sup>14</sup> for absolute immune responses were not met for the B strains. Does ACV have any concerns about this result?

The single pivotal study showed that aQIV was non-inferior to separate aTIVs for the antigen strains included in the tested vaccine. This study was conducted during a single influenza season.

Substantial variability of immune response against B strains is not uncommon. The committee referred to Table 5 of the sponsor's responses to the TGA dated 11 April 2019.<sup>15</sup> The committee also referred to the literature review by Camilloni et al.,<sup>16</sup> where the B strain immunogenicity of aTIV in adults over 60 years varied from 10 to 89% across 25 studies conducted between 1992 and 2013. While seroprotection against A strains was shown in all but 2 studies, seroprotection against B strains was not reached in 7 studies.

Variability in the immunogenicity of A strains was also seen in the pivotal study: haemagglutination inhibition titer  $\geq 1:40$  was reached in 69% of subjects for A/H1N1 and 93% of subjects for A/H3N2.

The subgroup analyses confirmed similar immunogenicity of aQIV and aTIV in subjects of different age groups ( $\geq 65$  to 74,  $\geq 75$  to 84, and  $\geq 85$  years), gender, race, comorbidity status and previous influenza vaccination history.

2. Vaccine efficacy has not been assessed. Does the ACV support the registration of Flud Quad on the basis of the immunogenicity results from Study V118\_20 and the supportive immunogenicity and effectiveness data from aTIV studies?

<sup>14</sup>US FDA Center for Biologics Evaluation and Research (CBER) criteria for effectiveness include:

'For adults  $\geq 65$  years of age:

- The lower bound of the two-sided 95% CI for the percent of subjects achieving seroconversion for HI antibody should meet or exceed 30%.
- The lower bound of the two-sided 95% CI for the percent of subjects achieving an HI antibody titer  $\geq 1:40$  should meet or exceed 60%.

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-data-needed-support-licensure-seasonal-inactivated-influenza-vaccines>

<sup>15</sup> Table 5: 'Lower Bound of the 2-sided 95% Confidence Interval for Seroconversion Rate and proportion of Subjects with HI titer  $\geq 1:40$  - CBER Criteria for Licensure in 16 aTIV Single-Dose Studies Comparing aTIV with TIV at Post-vaccination (Day 21- 29) - Full Analysis Set' - see also Table 4 in this AusPAR.

<sup>16</sup> Camilloni B, Basileo M, Valente S, Nunzi E, Iorio AM. Immunogenicity of intramuscular MF59-adjuvanted and intradermal administered influenza enhanced vaccines in subjects aged over 60: A literature review. Hum Vaccin Immunother. 2015;11(3):553-63. doi: 10.1080/21645515.2015.1011562

The ACV noted that in the past immunogenicity has been accepted as a surrogate endpoint for efficacy of seasonal influenza vaccines, except in young children.

The committee noted that antibody response (immunogenicity) is not necessarily the best predictor of clinical efficacy in older adults, and there are limitations in the use of immunogenicity data as a surrogate for vaccine efficacy.

The ACV considered whether an adjuvanted quadrivalent vaccine might be regarded as a novel vaccine, for which efficacy would need to be demonstrated.<sup>17</sup> Given the mechanism and dose are similar to the aTIV, and the same adjuvant in the same quantity is used in the aQIV as the aTIV, the ACV felt that immunogenicity is probably an appropriate endpoint.

The ACV disagreed with the sponsor's response that routine pharmacovigilance activities will address the absence of vaccine effectiveness data. A vaccine effectiveness study would require the estimation of protection against influenza using a suitable study design, whether a cohort of vaccinated and unvaccinated individuals, or in a case-control study.

## Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Flud quad (inactivated quadrivalent influenza vaccine (surface antigen), adjuvanted) containing influenza virus surface antigens (haemagglutinin and neuraminidase) of each of four antigens representative of the influenza virus types expected to circulate in the Southern Hemisphere winter (specifically, 15 µg of influenza virus haemagglutinin from each of two A strains (A/H1N1 and A/H3N2) and two B strains (Yamagata lineage and Victoria lineage)), indicated for:

*Active immunisation against influenza in persons 65 years of age and older.*

## Specific conditions of registration applying to these goods

1. The Flud Quad European Union (EU)-Risk Management Plan (RMP) (version 1.0, dated 9 January 2019, data lock point 31 October 2018), with Australian Specific Annex (version 1.0, dated 17 January 2019), included with submission PM-2019-00120-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the

<sup>17</sup> See European Medicines Agency: Guideline on Influenza Vaccines 21 July 2016  
EMA/CHMP/VWP/457259/2014

registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

2. Batch Release Testing and Compliance with the Certified Product Details

It is a condition of registration that all independent batches of Flud Quad imported into Australia 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 Laboratories Branch, TGA.

For each independent batch of the product imported into Australia, the sponsor must supply the following:

- a. A completed Request for Release Form, available from [vaccines@health.gov.au](mailto:vaccines@health.gov.au).
- b. Complete summary protocols for manufacture and QC, including all steps in production.
- c. At least 20 (twenty) doses of the first consignment of each batch of Flud Quad with the Australian approved labels, PI and packaging
- d. At least 10 (ten) doses of any further consignment of each batch of Flud Quad with the Australian approved labels, PI and packaging
- e. Certificate of Release from a regulatory agency acting for the country of origin such as an OMCL (if available).
- f. Any reagents, reference material and standards required to undertake testing, as requested by Laboratories Branch, TGA.

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

3. Certified Product Details

An electronic copy of the Certified Product Details (CPD) as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) <https://www.tga.gov.au/guidance-7-certified-product-details> should be provided upon registration of the therapeutic good. In addition, an updated CPD, for the above products incorporating the approved changes is to be provided within one month of the date of approval letter. A template for preparation of CPD for biological prescription medicines and Vaccines can be obtained from the TGA website <https://www.tga.gov.au/form/certified-product-details-cpd-biological-prescriptionmedicines>. The CPD should be sent as a single bookmarked PDF document to [vaccines@health.gov.au](mailto:vaccines@health.gov.au) as soon as possible after registration/approval of the product or any subsequent changes as indicated above.

4. For all injectable products the Product Information must be included with the product as a package insert.

## Attachment 1. Product Information

The PI for Flud 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>](https://www.tga.gov.au/product-information-pi).

## **Therapeutic Goods Administration**

PO Box 100 Woden ACT 2606 Australia

Email: [info@tga.gov.au](mailto:info@tga.gov.au) Phone: 1800 020 653 Fax: 02 6232 8605

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