

## 5.16 INFLUENZA VACCINE

### Injection (0.5 mL)

### Flublok® Quadrivalent

### SANOFI-AVENTIS AUSTRALIA PTY LTD

#### 1 Purpose of submission

- 1.1 The Category 2 submission requested National Immunisation Program (NIP) listing for quadrivalent recombinant influenza vaccine (RIV4) for the prevention of influenza in people aged 65 years and over.
- 1.2 Listing was requested on the basis of a cost-consequence analysis versus the existing NIP-funded adjuvanted egg-based quadrivalent influenza vaccine (aQIV), also referred to as allV4e, Flud® Quad).
- 1.3 The submission claimed that the recombinant vaccine technology used in RIV4 has advantages over alternative egg- and cell-based approaches and requested a “technology premium” (refer to Paragraphs 6.29 to 6.40).
- 1.4 Table 1 shows the key components addressed by the submission.

**Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)**

| Component      | Description   |
|----------------|---|
| Population     | Adults aged ≥ 65 years  |
| Intervention   | A single 0.5 mL dose of RIV4, by IM injection every year  |
| Comparator     | A single 0.5 mL dose of aQIV, by IM injection every year  |
| Outcomes       | Efficacy: relative vaccine efficacy and comparative rate of influenza events<br>Immunogenicity: post-vaccination geometric mean titres for vaccine included strains<br>Safety: adverse events by type, severity and relationship to vaccination |
| Clinical claim | At least non-inferior comparative effectiveness, immunogenicity and safety.<br>The submission also claimed that RIV4 was associated with ‘technological advantages that are likely to translate into significant societal level benefits’.      |

Source: Table 1-1, p11 of the submission.

aQIV = adjuvanted egg-based quadrivalent influenza vaccine (Flud® Quadrivalent); IM = intramuscular; RIV4 = quadrivalent recombinant influenza vaccine (Flublok® Quadrivalent).

#### 2 Background

##### **Registration status**

- 2.1 RIV4 was registered on the Australian Register of Therapeutic Goods on 13 May 2021 for “active immunisation for the prevention of influenza disease caused by influenza virus types A and B contained in the vaccine. Flublok Quadrivalent is approved for use in persons 18 years of age and older.”

##### **Previous PBAC consideration**

- 2.2 There have been no previous PBAC considerations for RIV4.

2.3 Table 2 outlines relevant previous PBAC considerations of influenza vaccinations.

**Table 2: Relevant PBAC considerations for influenza vaccines**

| Vaccine  | Relevant PBAC considerations   |
|--|--|
| <b>≥ 65 year old cohort</b>                    |  |
| <b>aTIV</b><br>(Fluad®)                        | <b>Recommended March 2018 on the basis of a CMA versus QIVe</b><br><b>July 2019</b> Sought an increased price based on a claim of superiority over QIVe, but the price increase was not recommended as “the extent of benefit of the adjuvanted trivalent formulation over the non-adjuvanted quadrivalent vaccine was uncertain given the impact of the loss of the additional B strain differed across influenza seasons” (Para 7.1, aTIV PSD, July 2019 PBAC meeting).  |
| <b>aQIV</b><br>(aIIV4e)<br>(Fluad®<br>Quad)    | <b>Recommended August 2019, based on claim of non-inferiority versus aTIV</b><br>“The PBAC was of a mind to recommend aQIV on a cost-effectiveness basis to non-adjuvanted quadrivalent (QIV) influenza vaccine pending provision of a positive TGA Delegate’s Overview. The PBAC considered that aQIV would provide additional clinical effectiveness to QIV and the magnitude of the benefit would be similar to that for aTIV over TIV. As such, the economic analysis provided in the submission for aTIV versus TIV, could be relied on to determine the cost-effectiveness of aQIV versus QIV and aQIV was considered cost-effective at the proposed price” (Para 7.13, aQIV PSD, July 2019 PBAC meeting).   |
| <b>TIV-HD</b><br>(Fluzone high dose trivalent) | <b>Recommended March 2018 on the basis of a CMA versus QIVe</b><br><b>July 2018</b> Sought increased price on the basis of a CUA versus QIVe – not recommended.<br><b>November 2019</b> Sought increased price on the basis of a CUA versus QIVe, however the PBAC recommended TIV-HD on the basis of a <b>CMA versus aQIV</b> (which was recommended for NIP listing in August 2019).<br>“The PBAC recommended an increase in the price of TIV-HD...on the basis that, on balance, TIV-HD was at least as effective as aQIV. The PBAC considered a claim of superiority versus aQIV could not be adequately supported by the clinical evidence presented and therefore a CMA in which TIV-HD was the same price as aQIV would be appropriate” (Para 7.1, TIV-HD PSD, November 2019 PBAC meeting). |
| <b>&lt; 65 year old cohort</b>                 |  |
| <b>QIVc</b><br>(IIV4c)<br>(Flucelvax®<br>Quad) | <b>September 2022</b> For particular individuals aged < 65 years:<br>“...the cost-effectiveness of QIVc would be acceptable with a price premium compared to egg-based quadrivalent influenza virus vaccines and the acknowledgment of potential benefits associated with the diversification of vaccine manufacturing.”<br>“The PBAC acknowledged there were advantages of cell-based vaccine production technology over the egg-based technology and in diversifying vaccine production platforms. The PBAC noted that cell-based technology may allow faster start-up of vaccine production when needed (for example in the event of a pandemic) and production would not be dependent on egg supply” (Paras 7.1 and 7.2, QIVc PSD, September 2022 PBAC meeting).                               |

Source: compiled during preparation of the evaluation.

aQIV = adjuvanted quadrivalent influenza vaccine (Fluad® Quadrivalent); aTIV = adjuvanted trivalent influenza vaccine (Fluad® Quadrivalent); CMA = cost-minimisation analysis; CUA = cost-utility analysis; Para = paragraph; PSD = Public Summary Document; QIVc = cell-based quadrivalent subunit influenza virus vaccine (Flucelvax® Quad), QIVe = egg-based quadrivalent subunit influenza virus vaccine; TIV-HD = high dose inactivated trivalent influenza vaccine (Fluzone High-Dose)

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

### 3 Requested listing

3.1 The submission requested that RIV4 be added as a new item on the Vaccines Determination, under the same circumstances as aQIV: “Vaccine may be provided to a person who is at least 65 years of age”.

| Name, Restriction, Manner of administration and form   | Requested Nationally Negotiated Price | Proprietary Name and Manufacturer                      |
|--|---------------------------------------|--|
| Quadrivalent Recombinant Influenza Vaccine (INFLUENZA HAEMAGGLUTININ RECOMBINANT) Solution for I.M injection 180 microgram in 0.5 mL | \$                                    | Flublok® Quadrivalent Sanofi-Aventis Australia Pty Ltd |

| Category/Program:  | NIP:   |
|--|--|
| Groups eligible for the requested NIP listing of Flublok® Quadrivalent | Vaccine may be provided to a person who is at least 65 years of age. |
| Number and timing of doses   | A single Flublok® Quadrivalent (0.5 mL) injection per calendar year  |

NIP: National Immunisation Program

3.2 The submission requested that the determination for quadrivalent recombinant influenza vaccine (Flublok® Quadrivalent; RIV4) should align with the current NIP listing of adjuvanted egg-based quadrivalent influenza vaccine (Fluad® Quadrivalent; aQIV) for persons aged at least 65 years of age. The PBAC considered this was appropriate.

#### People aged < 65 years

3.3 The submission stated “A request for advice from the Australian Technical Advisory Group on Immunisation (ATAGI) which was considered at its August 2023 meeting, contemplated a much broader NIP listing for RIV4, also incorporating adults aged 50-64 years, with and without risk factors for severe influenza. However, based on the advice received, only the narrower NIP listing, for use in the established population of adults aged 65 years or older is being requested of the PBAC at this time. This is because the adult population of 65 years or older is considered to have the greatest clinical need as they are disproportionately affected by complications and severe outcomes resulting from influenza infection, including hospitalisation and death. A subsequent submission, addressing the population(s) aged 50-64 years of age may be progressed during 2024, subject to the completion of appropriate clinical, economic and financial analyses”.

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

## **4 Population and disease**

- 4.1 Influenza is an acute viral infection of the respiratory tract. There are four types of influenza viruses: influenza A, B, C, and D but only influenza A and B viruses cause clinically important human disease and seasonal epidemics. Beyond the acute symptoms, influenza is also associated with complications including (but not limited to) acute bronchitis, pneumonia (both primary viral and secondary bacterial pneumonia), and cardiovascular complications including myocarditis and pericarditis.
- 4.2 Influenza viruses are coated with two proteins, haemagglutinin (HA) and neuraminidase (NA). Antibodies against these proteins provide protection against infection. As influenza viruses replicate, there are continual changes from mutations

in the genes encoding the HA and NA surface proteins, called antigenic drift. These changes accumulate and existing antibodies become less effective at neutralising the virus. Therefore, protection by vaccination requires annual dosing with updated vaccines.

- 4.3 In Australia, vaccine composition is decided by the TGA, with advice from the Australian Influenza Vaccine Committee (AIVC), which examines, among other things, epidemiology, antigenic and genetic characteristics of recent influenza isolates circulating in Australia and the southern hemisphere. The AIVC meets after the annual World Health Organization (WHO) strain composition meeting and its advice generally aligns with the WHO recommendations, unless there are scientific or practical reasons for variations<sup>1</sup>. Antigenic drift, and mismatch in vaccine and circulating viruses, means vaccine effectiveness can vary across (and within) seasons.
- 4.4 The traditional manufacturing process for influenza vaccines utilises fertilised chicken eggs. During this process mutations can occur in the receptor binding region of HA, which can lead to antigenic mismatch to circulating viruses, and reduced vaccine effectiveness known as egg adaptation. This is a particular problem for influenza A/H3N2 and B viruses.
- 4.5 RIV4 is manufactured using a baculovirus overexpression system to express the HA antigen in an insect cell line. This process yields HA that is genetically identical to the selected (wild-type) influenza strains, generating HA proteins that are structurally and functionally equivalent to the circulating wild-type strain. The submission stated this “assures the vaccine viral strains represent antigens that are an exact match to the WHO selected strains which induce the desired humoral immune response.”
- 4.6 RIV4 contains 45 µg of HA protein from each of four influenza strains (A/H1N1, A/H3N2, B/Victoria lineage, B/Yamagata lineage). This is three times the amount of HA as contained in standard dose egg- or cell-based inactivated vaccines, but less than the 60 µg for each strain contained in the high-dose quadrivalent vaccine” (ATAGI, pre-submission advice).

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

## **5 Comparator**

- 5.1 The submission nominated aQIV as the main comparator. In its pre-submission advice ATAGI considered this appropriate for the requested population.
- 5.2 While the NIP specifies three influenza vaccines that can be provided through the NIP for persons aged 65 and over (aQIV, high dose inactivated trivalent influenza vaccine (TIV-HD, Fluzone<sup>®</sup> High Dose), and adjuvanted trivalent influenza vaccine (aTIV,

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<sup>1</sup> <https://www.tga.gov.au/aivc-terms-reference>

Fluad®), the submission stated that only aQIV is currently procured and supplied through the NIP in this population.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **6 Consideration of the evidence**

### ***Sponsor hearing***

6.1 There was no hearing for this item.

### ***Consumer comments***

6.2 The PBAC noted and welcomed the input from three organisations via the Consumer Comments facility on the PBS website. The comments described a range of benefits of vaccination with RIV4 including that it would provide an additional option for people aged  $\geq 65$  years and the recombinant technology may be associated with potential manufacturing advantages including a reduced requirement for egg-based manufacturing.

6.3 The PBAC noted the advice received from Lung Foundation Australia which outlined that RIV4 would 'enable an alternative line of supply' and outlined the importance of access to effective influenza vaccines for individuals aged  $\geq 65$  years.

6.4 The PBAC noted that this advice was supportive of the evidence provided in the submission.

### ***Clinical studies***

6.5 The submission did not identify any studies comparing RIV4 and aQIV, which the ATAGI pre-submission advice listed as a key translation issue.

6.6 The submission noted that the PBAC had previously considered that "aQIV would be at least non-inferior to adjuvant trivalent vaccine (aTIV)" (Paragraph 7.20, aTIV and aQIV Public Summary Document (PSD), August and July 2019 PBAC meetings) and thus presented studies that compared RIV4 with aTIV, along with an immunogenicity study comparing aQIV and aTIV. As such, the submission assumed that studies comparing the effectiveness of "RIV4 with aTIV could be extrapolated to the comparison of RIV4 with aQIV". No indirect comparisons were presented.

6.7 As outlined in Table 3, the submission included data from:

- Izurieta 2021, which was an observational study comparing five vaccines: RIV4; aTIV; QIVe; QIVc; and TIV-HD. The study included approximately 12.8 million individuals aged  $\geq 65$  years in the United States during the 2019-20 Northern Hemisphere influenza season.
- Izurieta 2020 (a parallel publication to Izurieta 2021, but for the 2018-19 influenza season). However, Izurieta 2020 did not include RIV4 in the inverse probability of treatment weighting (IPTW) adjusted relative vaccine effectiveness (rVE) analysis

due to power constraints, as only 2% of the cohort received RIV4 in 2018-19 (i.e., only unadjusted outcome rates were reported). The ATAGI post-submission advice stated “Overall, this publication provides limited information on the effectiveness of RIV4 and is superseded by the subsequent Izurieta 2021 publication that provides statistical comparisons between vaccines during the 2019-2020 influenza season.”

- Immunogenicity data from Belongia et al 2020 and Cowling et al 2020 which compared RIV4 and aTIV (along with other vaccines, but not aQIV); and
- Immunogenicity data from Essink et al 2020, which compared aQIV and aTIV. The submission stated that this was a publication of the trial (Trial V118\_20), which was used to support the non-inferiority of aQIV to aTIV in the PBAC’s July 2019 consideration. The PSD for that consideration states “The PBAC accepted that aQIV would be at least non-inferior to aTIV based on the immunogenicity results from Trial V118\_20”, but also noted that the “ATAGI noted this study (Essink et al 2020) found aQIV superior to aTIV for the B strain not included in each aTIV” (Paragraphs 7.20 and 6.46, aTIV and aQIV PSD, August and July 2019 PBAC meeting).

6.8 The latter three immunogenicity studies were not included in the ATAGI pre-submission advice. The evaluation considered that these studies appeared to have been included in the PBAC submission to address concerns in the ATAGI pre-submission advice that “The decision to exclude the immunogenicity studies from the submission was not adequately justified as a comprehensive analysis of immunogenicity studies could be informative given the limitations of the available clinical data (particularly regarding the impact of different circulating strains and vaccine mismatch)”. Further, the ATAGI pre-submission advice stated “Overall, the generalisability of vaccine efficacy estimates from the clinical studies to the Australian clinical setting is unclear. Additional data (particularly immunogenicity outcomes) may be informative in translating the evidence to the Australian clinical setting.” ATAGI commented on these studies in its post-submission advice.

**Table 3: Studies and associated reports presented in the submission**

| Trial ID   | Protocol title/ Publication title  | Publication citation   |
|--|--|--|
| <b>Observational studies</b>   |  |  |
| Izurieta et al., 2021  | Izurieta et al. Comparative Effectiveness of Influenza Vaccines Among US Medicare Beneficiaries Ages 65 Years and Older During the 2019–2020 Season  | Clinical Infectious Diseases 2021; 73: e4251–e4259.  |
| Izurieta et al., 2020  | Relative Effectiveness of Influenza Vaccines Among the United States Elderly, 2018-2019.   | The Journal of infectious diseases, 222(2), 278–287.                                       |
| <b>Direct randomised controlled trials (immunogenicity outcomes and safety)</b>  |  |  |
| Belongia et al., 2020<br>NCT02872311   | Clinical trial to assess immunogenicity of high-dose, adjuvanted, and recombinant influenza vaccines against cell-grown A(H3N2) viruses in adults 65 to 74 years, 2017-2018.                                 | Vaccine 38(15): 3121–3128.   |
| Cowling, Perera, et al., 2020<br>Cowling, Thompson, et al., 2020.<br>NCT03330132 | Comparative Immunogenicity of Several Enhanced Influenza Vaccine Options for Older Adults: A Randomized, Controlled Trial.<br><br>Comparative Reactogenicity of Enhanced Influenza Vaccines in Older Adults. | Clin Infect Dis. 2020 Oct 23;71(7):1704–1714.<br><br>J Infect Dis. 2020; 222(8):1383–1391. |
| Essink et al., 2020<br>NCT03314662   | Immunogenicity and safety of MF59-adjuvanted quadrivalent influenza vaccine versus standard and alternate B strain MF59-adjuvanted trivalent influenza vaccines in older adults                              | Vaccine 38 (2020) 242–250  |

Source: Table 2-3, p22 of the submission.

### 6.9 Key features of the included evidence are outlined in Table 4.

**Table 4: Key features of the included evidence**

| Trial  | N   | Design/ duration  | Risk of bias | Patient population           | Outcome(s)  |
|--|---|---|--------------|------------------------------|---|
| <b>RIV4 versus aTIV (and QIVe vs QIVc vs TIV-HD)</b> |   |   |              |                              |   |
| Izurieta et al., 2021                                | 12.8 million (5% received RIV4)               | Retrospective cohort using US Medicare claims data for the 2019-2020 influenza season | Uncertain    | ≥ 65 years                   | rVE, influenza hospital encounters, influenza inpatient stays |
| Izurieta et al., 2020                                | 12.8 million (2% received RIV4)               | Retrospective cohort using US Medicare claims data for the 2017-2018 influenza season | Uncertain    | ≥ 65 years                   | rVE, influenza hospital encounters, influenza inpatient stays |
| <b>RIV4 versus aTIV (and TIV-HD)</b>                 |   |   |              |                              |   |
| Belongia et al., 2020                                | 89  | R, controlled<br>2 year   | NA           | Age 65-74                    | Immunogenicity, rate of influenza events                      |
| <b>RIV4 and aTIV (and QIVe versus TIV-HD)</b>        |   |   |              |                              |   |
| Cowling 2020   | 1,861<br>200 pairs in immunogenicity analysis | R, DB,<br>2017/18 northern hemisphere flu season                                      | NA           | Age 65-82 years<br>Hong Kong | Immunogenicity, rate of influenza events, safety              |
| <b>aQIV versus aTIV-1, versus aTIV-2</b>             |   |   |              |                              |   |
| Essink et al., 2020                                  | 1,778   | R, DB<br>2017/18 northern hemisphere flu season                                       | NA           | ≥ 65 years                   | Immunogenicity, safety  |

Source: Sections 2.3 and 2.4, pp 24-38 of the submission.

aQIV = adjuvanted quadrivalent influenza vaccine (Fluad Quad); aTIV = adjuvanted trivalent influenza vaccine (Fluad); DB = double blind; NA = not assessed; QIVc = cell-based quadrivalent subunit influenza virus vaccine (Flucelvax® Quad), QIVe = egg-based quadrivalent subunit influenza virus vaccine; R = randomised; RIV4 = quadrivalent recombinant influenza vaccine (Flublok Quad); rVE = relative vaccine effectiveness; TIV-HD = high dose inactivated trivalent influenza vaccine (Fluzone High-Dose).

### 6.10 The ATAGI pre-submission advice stated “the Izurieta 2021 study was based on a retrospective analysis of US Medicare claims data with an uncertain risk of bias. The

study attempted to minimise the risk of bias by using an IPTW approach which utilised propensity weighting to adjust for differences between treatment groups (demographics, region of residence, month of vaccination, chronic health conditions, frailty, prior medical encounters and use of preventative services). The publication noted that after adjustment, most covariates were well-balanced between treatment groups with the exception of month of vaccination (with RIV4 vaccination typically occurring later in the influenza season compared to the other vaccines). However, the publication acknowledged that the potential for residual confounding due to unmeasured variables could not be excluded.” Other issues previously identified with parallel publications from previous influenza seasons (e.g. Izurieta 2017-18 used to support the PBAC consideration of TIV-HD) included: the applicability given seasonal variation of influenza strains (e.g. due to egg-adaptation); and the exclusion of aged care facility residents. A further limitation was that lack of access to virological case confirmation.

6.11 With regards to the immunogenicity studies, the ATAGI post-submission advice noted:

- Neither Belongia 2020 nor Cowling 2020 provided comparative immunogenicity outcomes of RIV4 versus adjuvant quadrivalent vaccines in individuals aged  $\geq 65$  years.
- There appeared to be incomplete reporting of outcomes in Belongia 2020, with the publication only reporting microneutralisation assay results for the H3N2 strain at Day 28, while the trial protocol indicated that analyses of all strains were conducted using both haemagglutination inhibition and microneutralisation assays at both Day 28 and Month 6.
- The robustness of Belongia 2020 was unclear as the sub-study comparing RIV4 to other enhanced vaccines was based on a small sample size without formal statistical power calculations and did not include any adjustment for multiplicity of testing despite a large number of comparisons being conducted. Additionally, Cowling 2020 was based on a selected subset of 200 individuals from each treatment arm rather than all randomised individuals (although characteristics appeared broadly similar between the first-year immunogenicity subset and overall trial population) and the analyses were only powered to detect statistical differences between the enhanced vaccines (RIV4, aTIV and TIV-HD) versus QIVe.

### ***Comparative effectiveness***

6.12 The unadjusted results of Izurieta 2021 (2019-20 Northern Hemisphere influenza season) for the outcomes of influenza hospital encounters and inpatient stays are presented in Table 5.

Table 5: Unadjusted outcome rates in 2019–2020 influenza season, Izurieta 2021

| Cohort                               | Percent of cohort | Number of events | Total person time <sup>a</sup> | Outcome rate (95% CI) <sup>b</sup> |
|--------------------------------------|-------------------|------------------|--------------------------------|------------------------------------|
| <b>Influenza hospital encounters</b> |                   |                  |                                |                                    |
| RIV4                                 | 5.0%              | 1,179            | 770                            | 1.53 (1.44, 1.62)                  |
| QIVe                                 | 12.3%             | 3,956            | 1,832                          | 2.16 (2.09, 2.23)                  |
| QIVc                                 | 6.4%              | 2,092            | 965                            | 2.17 (2.08, 2.26)                  |
| aTIV                                 | 20.1%             | 4,991            | 3,017                          | 1.65 (1.61, 1.70)                  |
| TIV-HD                               | 56.2%             | 14,612           | 8,429                          | 1.73 (1.71, 1.76)                  |
| <b>Influenza inpatient stays</b>     |                   |                  |                                |                                    |
| RIV4                                 | 5.0%              | 640              | 770                            | 0.83 (0.77, 0.90)                  |
| QIVe                                 | 12.3%             | 2,309            | 1,833                          | 1.26 (1.21, 1.31)                  |
| QIVc                                 | 6.4%              | 1,235            | 965                            | 1.30 (1.23, 1.37)                  |
| aTIV                                 | 20.1%             | 2,783            | 3,018                          | 0.92 (0.89, 0.96)                  |
| TIV-HD                               | 56.2%             | 8,192            | 8,433                          | 0.97 (0.95, 0.99)                  |

Source: Table 2-19, p39 of the submission.

aQIV = adjuvanted quadrivalent influenza vaccine (Fluad Quad); aTIV = adjuvanted trivalent influenza vaccine (Fluad); QIVc = cell-based quadrivalent subunit influenza virus vaccine (Flucelvax® Quad), QIVe = egg-based quadrivalent subunit influenza virus vaccine; RIV4 = quadrivalent recombinant influenza vaccine (Flublok Quad); TIV-HD = high dose inactivated trivalent influenza vaccine (Fluzone High-Dose).

<sup>a</sup> Person time is in 10,000 person weeks.

<sup>b</sup> Outcome rates are calculated in the high influenza period only.

6.13 The IPTW-adjusted pairwise rVE estimates from Izurieta 2021 are in Table 6.

Table 6: IPTW adjusted pairwise rVE estimates for 2019–2020 influenza season, Izurieta 2021

| Cohort                               | Reference group, relative vaccine efficacy |                           |                         |                            |
|--------------------------------------|--|---------------------------|-------------------------|----------------------------|
|                                      | QIVe<br>% (95% CI)                         | aTIV<br>% (95% CI)        | TIV-HD<br>% (95% CI)    | RIV4<br>% (95% CI)         |
| <b>Influenza hospital encounters</b> |  |                           |                         |                            |
| QIVc                                 | 2.8 (-2.8, 8.2)                            | <b>-5.8 (-11.7, -0.3)</b> | -4.2 (-9.4, 0.8)        | <b>-12.1 (-20.6, -4.2)</b> |
| RIV4                                 | <b>13.3 (7.4, 18.9)</b>                    | 5.6 (-0.6, 11.4)          | <b>7.0 (1.4, 12.4)</b>  |                            |
| TIV-HD                               | <b>6.8 (3.3, 10.1)</b>                     | -1.6 (-4.8, 1.6)          |                         |                            |
| aTIV                                 | <b>8.2 (4.2, 12.0)</b>                     |                           |                         |                            |
| <b>Influenza inpatient stays</b>     |  |                           |                         |                            |
| QIVc                                 | 3.7 (-3.9, 10.7)                           | -3.4 (-11.0, 3.8)         | -3.5 (-9.4, 0.8)        | <b>-15.7 (-27.7, -4.8)</b> |
| RIV4                                 | <b>16.8 (9.0, 23.8)</b>                    | <b>10.7 (2.7, 17.9)</b>   | <b>10.6 (3.1, 17.4)</b> |                            |
| TIV-HD                               | <b>6.9 (2.3, 11.4)</b>                     | 0.1 (-1.4, 4.2)           |                         |                            |
| aTIV                                 | <b>6.8 (1.4, 11.9)</b>                     |                           |                         |                            |

Source: Table 2-20, p39 of the submission

aQIV = adjuvanted quadrivalent influenza vaccine (Fluad Quad); aTIV = adjuvanted trivalent influenza vaccine (Fluad); IPTW = inverse probability of treatment weighting; QIVc = cell-based quadrivalent subunit influenza virus vaccine (Flucelvax® Quad), QIVe = egg-based quadrivalent subunit influenza virus vaccine; RIV4 = quadrivalent recombinant influenza vaccine (Flublok Quad); rVE = relative vaccine effectiveness; TIV-HD = high dose inactivated trivalent influenza vaccine (Fluzone High-Dose).

**Bold** indicates values that are statistically significant.

6.14 In the IPTW-adjusted pairwise analysis, there was no statistically significant difference in rVE between RIV4 and aTIV for the outcome of influenza hospital encounters (5.6%, 95% CI: -0.6%, 11.4%), while RIV4 was associated with a statistically significant improvement in influenza inpatient stays versus aTIV (10.7%, 95% CI: 2.7%, 17.9%).

6.15 The ATAGI pre-submission advice stated “The submission argued that vaccine efficacy estimates for trivalent adjuvanted vaccine could be used as a proxy for quadrivalent adjuvanted vaccine on the basis that quadrivalent vaccines were unlikely to be advantaged during the 2019-2020 Northern Hemisphere influenza season (which was

dominated by the A/H1N1 and B/Victoria strains that were common to both the trivalent and quadrivalent vaccines). Therefore, the submission argued that RIV4 was non-inferior to aQIV based on vaccine efficacy.”

- 6.16 The ATAGI pre-submission advice further stated “The PBAC has previously considered that there are differences between adjuvanted trivalent and quadrivalent vaccines with the PBAC noting that adjuvanted trivalent vaccine was non-inferior to egg-based quadrivalent vaccines while adjuvanted quadrivalent vaccines were superior to egg-based quadrivalent vaccines in individuals  $\geq 65$  years (Paragraphs 7.8 and 7.14, adjuvant trivalent and quadrivalent influenza vaccine Public Summary Document, August 2019 PBAC meeting). Therefore, it is unclear whether the current evidence is sufficient to support a non-inferiority claim between RIV4 and aQIV.” Refer to Paragraphs 6.23 to 6.25 (‘Immunogenicity studies: aQIV versus aTIV’).
- 6.17 ATAGI concluded “The claim of ‘at least’ equivalent vaccine effectiveness [i.e. that RIV4 can be regarded as at least as effective as aQIV in those aged  $\geq 65$  years] was based on the assumption that the relative vaccine efficacy of adjuvant trivalent vaccine versus RIV4 in the Izurieta study could be used as a proxy for the relative vaccine efficacy of adjuvant quadrivalent vaccine versus RIV4. ATAGI noted that there was only limited circulation of B/Yamagata in the 2019-2020 influenza season and also noted that there has been only sporadic detection of this strain after the introduction of infection control measures associated with the COVID-19 pandemic (there are currently only three influenza strains in common circulation: A/H1N1, A/H3N3, B/Victoria). Based on the available data, ATAGI had reasonable confidence that RIV4 is ‘at least’ equivalent to adjuvanted vaccines in this population but was less confident that the available data were sufficient to support a claim of superiority.”

Immunogenicity studies: RIV4 versus aTIV

- 6.18 The results from Belongia et al 2020 for the pairwise comparison of geometric mean fold rise, by vaccine group and strain, are summarised in Table 7.

**Table 7: Pairwise comparison of geometric mean fold rise (GMFR) by vaccine group and strain.**

| A(H3N2) strain  | GMFR (95% CI) |               |               | p-value            |                   |
|---|---------------|---------------|---------------|--------------------|-------------------|
|   | TIV-HD        | aTIV          | RIV4          | RIV4 versus TIV-HD | RIV4 versus aTIV  |
| A/Hong Kong/4801/2014<br>HK4801 (clade 3c.2a)           | 1.6 (1.3-1.8) | 1.6 (1.3-2.0) | 2.0 (1.7-2.5) | <b>0.04</b>        | 0.10              |
| A/Singapore/INFIMH-16-0019/2016<br>SI16 (clade 3C.2a.1) | 1.4 (1.1-1.8) | 1.7 (1.4-2.2) | 3.3 (2.4-4.5) | <b>0.0001</b>      | <b>0.002</b>      |
| A/Kentucky/29/2017<br>KY29 (clade 3C.2a2)               | 1.6 (1.2-2.0) | 1.6 (1.2-2.0) | 3.5 (2.7-4.7) | <b>&lt;0.0001</b>  | <b>&lt;0.0001</b> |
| A/Kansas/14/2017<br>KS14 (clade 3c.3a)                  | 1.3 (1.1-1.6) | 1.7 (1.3-2.1) | 2.9 (2.0-4.3) | <b>0.0004</b>      | <b>0.01</b>       |

Source: Table 2-25, p42 of the submission

aTIV = adjuvanted trivalent influenza vaccine (Fluad); CI = confidence interval; GMFR = geometric mean fold rise; RIV4 = quadrivalent recombinant influenza vaccine (Flublok Quad); TIV-HD = high dose inactivated trivalent influenza vaccine (Fluzone High-Dose)

**Bold** indicates values that are statistically significant.

- 6.19 RIV4 was associated with a greater geometric mean fold rise against three of the representative circulating viruses (i.e. SI16 (clade 3C.2a1), KY29 (clade 3C.2a2) and KS14 (clade 3c.3a) compared with either TIV-HD or aTIV. Overall, the study authors concluded that RIV4 generated a higher level of cross-protective antibodies against antigenically advanced viruses compared to egg-derived vaccines in older adults. However, the authors further stated that the mechanism and clinical relevance remained unclear, particularly since post vaccination titres were relatively low in all groups.
- 6.20 The results from Cowling et al 2020 for the comparison of pre- and post-vaccination antibody titres and the corresponding mean fold rises across vaccines is summarised in Table 8.

Table 8: Summary of pre- and post-vaccination antibody titres and fold rises by group

| Assay Strain                                    | QIVe<br>n=200        | aTIV<br>n=200        | TIV-HD<br>n=200      | RIV4<br>n=200        |
|---|----------------------|----------------------|----------------------|----------------------|
|   | Estimate<br>(95% CI) | Estimate<br>(95% CI) | Estimate<br>(95% CI) | Estimate<br>(95% CI) |
| <b>HAI</b>                                      |                      |                      |                      |                      |
| <b>A/Michigan/45/2015 (H1N1)</b>                |                      |                      |                      |                      |
| Day 0 GMT                                       | 17 (14–20)           | 17 (15–20)           | 20 (17–24)           | 16 (14–19)           |
| Day 30 GMT                                      | 69 (58–83)           | <b>94 (78–114)</b>   | <b>125 (102–152)</b> | 85 (69–105)          |
| Mean fold rise from D0 to D30                   | 4.1 (3.5–4.9)        | <b>5.5 (4.6–6.6)</b> | <b>6.1 (5.1–7.3)</b> | <b>5.3 (4.4–6.3)</b> |
| % with ≥4-fold rise from D0 to D30 <sup>b</sup> | 42% (36–50%)         | <b>60% (53–67%)</b>  | <b>59% (52–66%)</b>  | <b>60% (53–67%)</b>  |
| <b>HAI</b>                                      |                      |                      |                      |                      |
| <b>A/Hong Kong/4801/2014 (H3N2) egg-like</b>    |                      |                      |                      |                      |
| Day 0 GMT                                       | 46 (39–56)           | 49 (41–59)           | 45 (38–54)           | 54 (45–64)           |
| Day 30 GMT                                      | 158 (135–186)        | <b>207 (178–241)</b> | <b>214 (183–250)</b> | <b>254 (218–295)</b> |
| Mean fold rise from D0 to D30                   | 3.4 (2.8–4.1)        | <b>4.2 (3.5–5.1)</b> | <b>4.7 (3.9–5.7)</b> | <b>4.7 (3.9–5.7)</b> |
| % with ≥4-fold rise from D0 to D30 <sup>a</sup> | 41% (34–48%)         | 48% (40–55%)         | <b>54% (46–61%)</b>  | <b>56% (48–63%)</b>  |
| <b>Microneutralization</b>                      |                      |                      |                      |                      |
| <b>A/Hong Kong/4801/2014 (H3N2) cell-like</b>   |                      |                      |                      |                      |
| Day 0 GMT                                       | 38 (31–46)           | 43 (35–53)           | 34 (28–41)           | 48 (39–59)           |
| Day 30 GMT                                      | 87 (72–106)          | <b>125 (102–152)</b> | <b>116 (95–141)</b>  | <b>223 (189–263)</b> |
| Mean fold rise from D0 to D30                   | 2.3 (2.0–2.6)        | <b>2.9 (2.5–3.4)</b> | <b>3.4 (2.9–4.0)</b> | <b>4.7 (3.9–5.6)</b> |
| % with ≥4-fold rise from D0 to D30 <sup>a</sup> | 28% (22–35%)         | <b>39% (32–46%)</b>  | <b>47% (40–54%)</b>  | <b>57% (50–64%)</b>  |
| <b>HAI</b>                                      |                      |                      |                      |                      |
| <b>B/Brisbane/60/2008 (Victoria lineage)</b>    |                      |                      |                      |                      |
| Day 0 GMT                                       | 24 (20–28)           | <b>31 (26–38)</b>    | <b>31 (26–37)</b>    | <b>29 (25–35)</b>    |
| Day 30 GMT                                      | 89 (75–105)          | 95 (81–112)          | <b>132 (112–157)</b> | 90 (76–107)          |
| Mean fold rise from D0 to D30                   | 3.7 (3.2–4.4)        | 3 (2.6–3.5)          | 4.2 (3.5–5.0)        | 3.1 (2.7–3.5)        |
| % with ≥4-fold rise from D0 to D30 <sup>a</sup> | 48% (41–56%)         | 44% (37–51%)         | 52% (45–60%)         | 44% (37–51%)         |
| <b>HAI</b>                                      |                      |                      |                      |                      |
| <b>B/Phuket/3073/2013b (Yamagata lineage)</b>   |                      |                      |                      |                      |
| Day 0 GMT                                       | 37 (31–44)           | 41 (35–49)           | 41 (34–50)           | 45 (38–54)           |
| Day 30 GMT                                      | 121 (104–141)        | <b>63 (54–74)</b>    | <b>68 (57–81)</b>    | 131 (111–155)        |
| Mean fold rise from D0 to D30                   | 3.3 (2.8–3.8)        | <b>1.5 (1.4–1.7)</b> | <b>1.6 (1.5–1.8)</b> | 2.9 (2.5–3.3)        |
| % with ≥4-fold rise from D0 to D30 <sup>a</sup> | 42% (36–50%)         | <b>12% (8–18%)</b>   | <b>15% (10–21%)</b>  | 42% (36–50%)         |

Source: Table 2-26, p 43 of the submission; Table 3, p1709 Cowling et al 2020.

aTIV = adjuvanted trivalent influenza vaccine (Fluad); CI = confidence interval, D = day; GMT = geometric mean titre, H = hemagglutinin; HAI = hemagglutination inhibition assay; MN = microneutralization assay; Prop = proportion; QIVe = egg-based quadrivalent subunit influenza virus vaccine; RIV4 = quadrivalent recombinant influenza vaccine (Flublok Quad); TIV-HD = high dose inactivated trivalent influenza vaccine (Fluzone High-Dose).

**Bold** indicates values that are significantly different from the corresponding value in the standard-dose group (QIVe).

Note that a B/Yamagata lineage virus was not included in the MF59-adjuvanted TIV and the high-dose TIV.

- 6.21 Mean fold rises (MFR) in hemagglutination inhibition assay (HAI) titres to egg-propagated A(H1N1) and A(H3N2) and cell-propagated A(H3N2) were statistically significantly higher in those who received enhanced vaccines (RIV4, TIV-HD and aTIV), compared to QIVe. The mean fold rise in microneutralisation to cell-propagated A(H3N2) was highest among RIV4 recipients (4.7, 95% CI: 3.9, 5.6), followed by TIV-HD (3.4, 95% CI: 2.9, 4.0) and aTIV (2.9, 95% CI: 2.5, 3.4) recipients, compared to QIVe recipients (2.3, 95% CI: 2.0, 2.6).
- 6.22 The ATAGI post-submission advice stated that the results of Belongia 2020 and Cowling 2020 “suggest that RIV4 has similar immunogenicity outcomes to other

enhanced vaccines for H1N1 but may be associated with improved immune response to some H3N2 virus strains. However, ATAGI noted some inconsistencies between studies for H3N2 immunogenicity outcomes using the microneutralisation assay (particularly the A/Hong Kong/4801/2014 strain) that were not adequately explained in the submission. Additionally, ATAGI noted that the H3N2 strains assessed in the included studies may not be representative of current circulating strains. Both recombinant and adjuvant vaccines had similar outcomes for the B/Victoria strain while RIV4 was associated with an improved immune response to the B/Yamagata strain (which was not included in the adjuvant trivalent vaccine).”

Immunogenicity studies: aQIV versus aTIV

6.23 The immunogenicity results of Essink 2020, which compared aQIV and aTIV, are presented in Table 9.

**Table 9: Summary of immunogenicity by strain in the per protocol set, Essink 2020.**

|   | aQIV                   | aTIV                  |
|---|------------------------|-----------------------|
| Number of participants                          | 872                    | 869                   |
| <b>A/H N1</b>                                   |                        |                       |
| Post vaccination titre $\geq 1:40$ , % (95% CI) | 69.38 (66.2 - 72.43)   | 70.31 (67.15 – 73.33) |
| Seroconversion, % (95% CI)                      | 35.21 (32.03 – 38.48)  | 38.43 (35.19 – 41.76) |
| <b>A/H3N2</b>                                   |                        |                       |
| Post vaccination titre $\geq 1:40$ , % (95% CI) | 93.92 (92.12 – 95.41)) | 94.82 (93.13 – 96.20) |
| Seroconversion, % (95% CI)                      | 39.33 (36.08 – 42.67)  | 39.70 (36.43 – 43.04) |
| <b>B Victoria</b>                               |                        |                       |
| Post vaccination titre $\geq 1:40$ , % (95% CI) | 38.19 (34.95 – 41.51)  | 36.93 (32.38 – 41.65) |
| Seroconversion, % (95% CI)                      | 13.42 (11.22 – 15.86)  | 12.16 (9.24 – 15.60)  |
| <b>B Yamagata</b>                               |                        |                       |
| Post vaccination titre $\geq 1:40$ , % (95% CI) | 32.80 (29.69 – 36.03)  | 36.95 (32.39 – 41.69) |
| Seroconversion, % (95% CI)                      | 16.40 (14.00 - 19.03)  | 15.47 (12.20 – 19.23) |

Source: Table 2-28, p45 of the submission

aTIV = adjuvanted trivalent influenza vaccine (Fluad); GMFR = geometric mean fold rise; RIV4 = quadrivalent recombinant influenza vaccine (Flublok Quad); TIV-HD = high dose inactivated trivalent influenza vaccine (Fluzone High-Dose).

- 6.24 The submission stated that aQIV met the non-inferiority criteria for GMT ratios and seroconversion rate differences as compared to aTIV and met superiority criteria for the B strain that was absent from aTIV. As outlined in Paragraph 6.7, Essink 2020 was used in the PBAC’s July 2019 consideration to support the claim of non-inferior efficacy between aQIV to aTIV. The PSD for that consideration states “ATAGI post-submission advice, advised that ATAGI considered aQIV to be at least non-inferior to aTIV based on immunogenicity data from the single pivotal phase 3 trial [the clinical study report for Essink 2020] undertaken over a single season which demonstrated non-inferiority of aQIV to aTIV and another aTIV containing the alternative B strain in the first aTIV. ATAGI noted this study found aQIV superior to aTIV for the B strain not included in each aTIV” (Paragraph 6.46, aTIV and aQIV PSD, August and July 2019 PBAC meeting).
- 6.25 The ATAGI post-submission advice stated “Overall, the additional studies presented in the PBAC submission do not change ATAGI’s previous advice that RIV4 is ‘at least’ equivalent to adjuvant vaccines in individuals aged  $\geq 65$  years.”

## Comparative harms

6.26 Table 10 presents the adverse events reported in Cowling 2020, which was the only study presented that included safety data for RIV4.

**Table 10: Summary of adverse reactions (any severity) one day after vaccination, Cowling 2020**

|                           | QIVe<br>n=429 |       | aTIV<br>n=442 |       |         | TIV-HD<br>n=424 |       |         | RIV4<br>n=280 |       |         |
|---------------------------|---------------|-------|---------------|-------|---------|-----------------|-------|---------|---------------|-------|---------|
|                           | n             | %     | n             | %     | p-value | n               | %     | p-value | n             | %     | p-value |
| <b>Local reactions</b>    |               |       |               |       |         |                 |       |         |               |       |         |
| Tenderness                | 73            | 17.0% | 94            | 21.3% | 0.05    | 102             | 24.1% | 0.04    | 42            | 15.0% | 0.15    |
| Pain                      | 50            | 11.7% | 56            | 12.7% | 0.91    | 61              | 14.4% | 0.55    | 22            | 7.9%  | 0.12    |
| Swelling                  | 36            | 8.4%  | 39            | 8.8%  | 0.07    | 51              | 12.0% | <0.01   | 11            | 3.9%  | <0.01   |
| Redness                   | 14            | 3.3%  | 11            | 2.5%  | 0.51    | 15              | 3.5%  | 0.8     | 6             | 2.1%  | 0.46    |
| Itching                   | 9             | 2.1%  | 13            | 2.9%  | 0.52    | 9               | 2.1%  | 1       | 7             | 2.5%  | 0.8     |
| <b>Systemic reactions</b> |               |       |               |       |         |                 |       |         |               |       |         |
| Fatigue                   | 18            | 4.2%  | 30            | 6.8%  | 0.24    | 21              | 5.0%  | 0.29    | 9             | 3.2%  | 0.66    |
| Feverishness              | 6             | 1.4%  | 14            | 3.2%  | 0.16    | 10              | 2.4%  | 0.37    | 1             | 0.4%  | 0.25    |
| Muscle pain               | 12            | 2.8%  | 8             | 1.8%  | 0.16    | 6               | 1.4%  | 0.3     | 3             | 1.1%  | 0.23    |
| Nausea                    | 1             | 0.2%  | 5             | 1.1%  | 0.37    | 3               | 0.7%  | 0.43    | 2             | 0.7%  | 0.57    |
| Others                    | 30            | 7.0%  | 32            | 7.2%  | 0.43    | 38              | 9.0%  | 0.43    | 15            | 5.4%  | 0.8     |

Source: Table 2-29, p46 of the submission.

6.27 The submission stated that acute local reactions were less frequent or similar with RIV4 compared with QIVe whereas some acute local reactions were more frequent with aTIV and TIV-HD. Systemic adverse reactions occurred at similar frequencies in all groups. Cowling 2020 also reported adverse reactions at 1-2 days, 3-4 days, 7-9 days and 14-16 days after vaccination, and concluded that reactions typically lasted only a few days, and more than half had resolved within 2 days after vaccination.

6.28 While the submission did not provide longer-term safety data for RIV4, the TGA Delegate’s Overview noted that 10,353 adults (aged ≥ 18 years) were exposed to RIV4 (with the majority being ≥ 50 years old). The most common injection site reactions were local tenderness and local pain. The most common systemic reactions were headache, fatigue, muscle pain, and joint pain. The TGA Delegate concluded “The safety profile of RIV4 has been adequately characterised in adults. The exposure was adequate and there appears to be sufficient post-market experience.”

## Other benefits: Technology premium

6.29 The submission requested a “technology premium” for RIV4 due to:

- (i) the advantages that it has over alternative egg- and cell-based quadrivalent influenza vaccines;
- (ii) the potential benefits associated with the diversification of the vaccine manufacturing process; and
- (iii) to support investment in new vaccine technologies in Australia.

6.30 Comments from the ATAGI pre-submission advice regarding points (i) and (ii) are outlined below.

(i) Advantages versus alternative egg- and cell-based quadrivalent influenza vaccines

6.31 The ATAGI pre-submission advice stated

“The submission stated that there are three major technological advantages of RIV4 compared to other vaccines. First, the recombinant technology allows the unaltered, full-length viral sequence to be used, which eliminates the risk of viral reassortment during the process of viral growth in egg and cell culture that can result in vaccine mismatch. Second, the recombinant HA in RIV4 avoids structural weaknesses that may develop during the growth and purification process of traditional inactivated influenza vaccines in a non-target cell substrate. Third, the presence of uniform compact HA oligomers and the absence of extraneous proteins, viral RNA or process impurities results in lower reactogenicity. This is claimed to allow the vaccine to contain three times the dose of the HA antigen (180 µg) than QIVe and QIVc (60 µg) but with a similar safety profile to QIVe, without a higher rate of local and systemic reactions.”

“Low vaccine efficacy of a particular strain in the influenza vaccine may occur due to a mismatch between vaccine and wild virus. Such mismatches can result from viral adaptations during the vaccine manufacturing process, particularly noted in egg-based vaccines against H3N2 strains. The submission also suggested that these adaptations have also been observed in mammalian cell culture of influenza virus (Chen 2016, Lin 2017). However, the clinical importance of viral adaptation in cell cultures has not been clearly established.”

“The submission suggested that the absence of structural weaknesses in RIV4 that may develop during the growth and purification process of traditional inactivated influenza vaccines may be the reason why there appears to be greater cross-protection to H3N2 strains by RIV4 compared to adjuvanted or high-dose influenza vaccines (Belongia 2020; Richards 2020). The submission argued that the superior immunogenic responses to RIV compared to the high dose influenza vaccines used in these studies suggest that the differences are not solely due to the higher HA dose in the recombinant vaccine. The authors of the immunogenicity studies cited in the submission note that the mechanisms underlying the greater responses induced by the RIV4 vaccine are not yet clear. It should be noted that the submission did not provide a systematic assessment of immunogenicity studies as part of the clinical evidence.”

6.32 Overall, in its pre-submission advice, the ATAGI considered that “it is plausible that RIV4 has some benefits over standard dose quadrivalent influenza vaccines given the higher HA dose as well as advantages over egg-based vaccines in terms of avoiding adaptations (primarily affecting the A/H3N2 strain) during the manufacturing process.”

6.33 The ESC noted that the ATAGI post-submission advice stated: “the potential advantage in avoiding cell-based adaptations is based on laboratory findings and the clinical relevance of this difference is unclear”. Further, the PBAC considered that the claimed

advantages were not based on comparative clinical evidence, and agreed with the ATAGI post-submission advice that the clinical relevance was unclear.

(ii) Diversification of the vaccine manufacturing process

- 6.34 The PBAC submission stated “the technology also allows for faster adaptation, manufacturing and scale up than either egg- or cell- based alternatives, which may be invaluable in the context of a pandemic or supply shortage” and “introduction of another suitably effective influenza vaccine into the older adult influenza NIP will provide greater security and continuity of supply”.
- 6.35 In its pre-submission advice, the ATAGI stated it “is supportive of alternative platforms for manufacturing seasonal influenza vaccines, including those that are not egg based. The valuation of this benefit is outside of ATAGI’s remit and requires broader health policy discussions.”

Price premium relative to that recommended for QIVc versus QIVe

- 6.36 The submission requested a price premium of the “same quantum” as that previously recommended by the PBAC for QIVc over other NIP listed QIVe vaccines (in eligible populations >65 years) and used \$| as a proxy.
- 6.37 In its September 2022 consideration of QIVc, the PBAC advised that a price premium versus QIVe would be reasonable “for the potential advantages of cell-based vaccine production technology compared to egg-based technology” (Paragraph 7.11, QIVc PSD, September 2022 PBAC meeting). The PBAC noted that advantages of QIVc versus QIVe included: diversifying vaccine production platforms; cell-based technology may allow faster start-up of vaccine production when needed (for example in the event of a pandemic); and production would not be dependent on egg supply (Paragraph 7.2 QIVc PSD, September 2022 PBAC meeting).
- 6.38 The PBAC recalled that further context to this previous consideration included Paragraph 7.6 of the PSD, which states “Although the PBAC considered that the clinical claim of superior efficacy [versus QIVe] was plausible, it considered that the comparative benefit was difficult to quantify and subject to a moderate level of uncertainty” (Paragraph 7.6, QIVc PSD, September 2022 PBAC meeting). In this case, the PBAC noted the submission for RIV4 had not made a claim of superior efficacy versus the nominated comparator (aQIV) and considered that the data presented were did not demonstrate a clear clinical benefit of RIV4 versus aQIV
- 6.39 The evaluation considered it was unclear whether the relative magnitude of benefit of the recombinant vaccine technology used in RIV4 versus currently available vaccine technologies is of a similar magnitude to the advantages of cell-based vaccine production technology compared with (non-adjuvanted) egg-based technology. For example, the evaluation considered it was unclear whether the technology advantages claimed by the sponsor (outlined in Paragraph 6.29) are relevant given a cell-based vaccine is available in Australia (albeit in a different population), particularly in terms of diversification of vaccine production platforms and faster start-up of

production (outlined in Paragraph 6.29 points (ii) and (iii)). The ESC noted that the ATAGI post-submission advice stated: “Overall, given that recombinant and cell-based vaccines are currently proposed for different populations but share several potential advantages, ATAGI considered it may be reasonable to assume that both technologies provide similar manufacturing/technology advantages in their respective populations.”

- 6.40 The ATAGI post-submission advice noted that the submission claimed two potential manufacturing/technology advantages of recombinant vaccines compared with cell-based vaccines:
- Recombinant vaccines are ‘purer’ allowing for higher antigen doses without an increase in reactogenicity. The ATAGI post-submission advice considered “The higher antigen doses with recombinant versus cell-based vaccines may translate to improved immunogenicity and clinical outcomes.... However, QIVc is not NIP-funded for the elderly population and therefore the importance of this advantage is unclear.”
  - Recombinant vaccines may avoid adaptations that have been observed in mammalian cell culture of influenza virus. However, the ATAGI post-submission advice noted “the potential advantage in avoiding cell-based adaptations is based on laboratory findings and the clinical relevance of this difference is unclear.”

### **Benefits/harms**

- 6.41 A benefits and harms table is not presented as the submission made a claim of non-inferiority.

### **Clinical claim**

- 6.42 The submission described RIV4 as “at least non-inferior” in terms of comparative effectiveness, immunogenicity and safety to the currently listed and supplied vaccine, aQIV. This claim was adequately supported based on the ATAGI pre-submission advice which stated: “based on the available data, ATAGI has reasonable confidence that RIV4 is ‘at least’ equivalent to adjuvanted vaccines in this population”. Further, the ATAGI post-submission advice stated “Overall, the additional studies presented in the PBAC submission do not change ATAGI’s previous advice that RIV4 is ‘at least’ equivalent to adjuvant vaccines in individuals aged  $\geq 65$  years.”
- 6.43 The ATAGI pre-submission advice further stated that ATAGI was “less confident that the available data were sufficient to support a claim of superiority”.
- 6.44 The submission further stated RIV4 is expected to provide “important technological advantages” over aQIV. The ATAGI post-submission advice stated “Overall, given that recombinant and cell-based vaccines are currently proposed for different populations but share several potential advantages, ATAGI considered it may be reasonable to assume that both technologies provide similar manufacturing/technology advantages in their respective populations.” The ESC noted that the ATAGI post-submission advice

stated: “the potential advantage in avoiding cell-based adaptations is based on laboratory findings and the clinical relevance of this difference is unclear”.

- 6.45 Administration of RIV4 appeared to be associated with a similar incidence of adverse events one day after vaccination compared with aTIV, QIVe and TIV-HD, though no long-term safety data or comparative safety data versus aQIV were presented. The TGA Delegate (Delegate’s Overview, p18) had concluded: “The safety profile of RIV4 has been adequately characterised in adults. The exposure was adequate and there appears to be sufficient post-market experience.”
- 6.46 The PBAC considered that the claim of “at least non-inferior” comparative effectiveness and safety was reasonable.

### ***Economic analysis***

- 6.47 The submission requested a price for RIV4 of \$ [REDACTED] per dose based on the assumed confidential price of aQIV (\$) plus a \$ [REDACTED] technology premium (refer to Paragraphs 6.29 to 6.40). The Pre-Sub-Committee Response stated that the value of \$ [REDACTED] was an estimate only and clarified that the request was for a premium of the “same quantum” as that recommended by the PBAC for QIVc over QIVe (in the <65 years cohort).
- 6.48 The submission described this as a cost-consequence analysis.
- 6.49 The submission estimated the equi-effective doses as:

$$\text{RIV4 (1 x 0.5 mL) = aQIV (1 x 0.5 mL).}$$

### ***Vaccine cost/person/year***

- 6.50 The dose and frequency of RIV4 and aQIV is one dose (intramuscular) once per year for individuals aged 65 years and over.
- The proposed price of RIV4 was \$ [REDACTED] per individual per year, using the \$ [REDACTED] premium applied in the submission.
  - The submission assumed that the price of aQIV is \$ [REDACTED] per individual per year.

### ***Estimated NIP usage & financial implications***

- 6.51 This submission was not considered by DUSC. The submission used a market share approach.
- 6.52 The key inputs applied in the financial estimates are outlined in Table 11.

**Table 11: Key inputs for financial estimates**

| Parameter                                       | Value applied and source   | Comment  |
|---|--|--|
| Eligible population                             | Based on ABS 3222.0  |  |
| Influenza vaccine coverage rate ('uptake rate') | 63.1% in each year, based on 'almost complete' data for 2023 (1 March to 31 August 2023, inclusive) <sup>a</sup> reported by the National Centre for Immunisation Research and Surveillance (NCIRS). | The submission noted there has been annual variation in this rate during recent years. In its post-submission advice, ATAGI concluded that the data source was reasonable. The ATAGI also stated that the NCIRS data "suggest that influenza vaccination rates continue to be depressed compared to estimates prior to the pandemic. It is unclear based on the currently available data whether lower vaccination rates will persist over time or gradually increase to pre-pandemic levels. In addition, government-funded pharmacist administration of NIP funded vaccines from 1 January 2024 may affect influenza vaccine uptake, however the extent of the impact is uncertain. ATAGI considered the assumption of stable vaccination rates over the next 6 years (remaining at the 2023 rate) was uncertain, but may be reasonable in the absence of any other data." |
| Market share                                    | 50% in each year. Estimated. aQIV was assumed to have the remaining 50% of market share.   | The submission acknowledged a small number of individuals would receive standard quadrivalent influenza vaccine due to availability issues. The ATAGI post-submission advice stated the "assumption of a peak uptake of 50% may be reasonable... However, the assumption that RIV4 will achieve peak uptake in the first year of listing was not reasonable as it does not account for gradual uptake over time against a well-established comparator."  |
| MBS item: Level A                               | Administration costs. Assumed to be the same for each vaccine.   | No net impact on the MBS as the number of vaccinations was assumed to be unchanged.  |

Source: Table 4.1, p 55 of the submission.

<sup>a</sup> Australian Immunisation Register data as at 03 Sep 2023.

6.53 The estimated use and financial implications of listing RIV4 on the NIP, as provided in the submission, are outlined in Table 12.

**Table 12: Estimated use and financial implications**

|  | Year 1       | Year 2       | Year 3       | Year 4       | Year 5       | Year 6       |
|--|--------------|--------------|--------------|--------------|--------------|--------------|
| <b>Estimated extent of use</b>                   |              |              |              |              |              |              |
| Number of people eligible                        | <sup>1</sup> | <sup>1</sup> | <sup>1</sup> | <sup>1</sup> | <sup>1</sup> | <sup>1</sup> |
| Influenza vaccine coverage rate                  | 63.1%        | 63.1%        | 63.1%        | 63.1%        | 63.1%        | 63.1%        |
| Number of people vaccinated                      | <sup>2</sup> | <sup>2</sup> | <sup>2</sup> | <sup>2</sup> | <sup>2</sup> | <sup>2</sup> |
| Market share of RIV4                             | 50%          | 50%          | 50%          | 50%          | 50%          | 50%          |
| Number of doses of RIV4                          | <sup>3</sup> | <sup>3</sup> | <sup>3</sup> | <sup>3</sup> | <sup>3</sup> | <sup>3</sup> |
| <b>Vaccine costs</b>                             |              |              |              |              |              |              |
| RIV4 (\$)  |              |              |              |              |              |              |
| aQIV (\$)  |              |              |              |              |              |              |
| <b>Estimated financial implications of RIV4</b>  |              |              |              |              |              |              |
| Cost to NIP                                      | <sup>4</sup> | <sup>4</sup> | <sup>4</sup> | <sup>4</sup> | <sup>4</sup> | <sup>4</sup> |
| <b>Estimated financial implications for aQIV</b> |              |              |              |              |              |              |
| Cost to NIP                                      | <sup>5</sup> | <sup>5</sup> | <sup>5</sup> | <sup>5</sup> | <sup>5</sup> | <sup>5</sup> |
| <b>Net financial implications</b>                |              |              |              |              |              |              |
| Net cost to NIP                                  | <sup>6</sup> | <sup>6</sup> | <sup>6</sup> | <sup>6</sup> | <sup>6</sup> | <sup>6</sup> |

Source: Table 4.1, p55 of the submission, Table 4.4, p57 of the submission.

The redacted values correspond to the following ranges:

<sup>1</sup> 4,000,000 to < 6,000,000

<sup>2</sup> 3,000,000 to < 4,000,000

<sup>3</sup> 1,000,000 to < 2,000,000

<sup>4</sup> \$30 million to < \$40 million

<sup>5</sup> net cost saving

<sup>6</sup> \$0 to < \$10 million

6.54 The total net cost to the NIP of listing RIV4 was estimated to be \$0 to < \$10 million in Year 6, and a total of \$40 million to < \$50 million in the first 6 years of listing.

6.55 The submission estimated the market share for RIV4 would be 50% every year, with aQIV assumed to have the remaining 50% of the market. The ATAGI post-submission advice stated “In the absence of any other data, the assumption of a peak uptake of 50% may be reasonable given the clinical claim of ‘at least’ non-inferior efficacy and similar safety. However, the assumption that RIV4 will achieve peak uptake in the first year of listing was not reasonable as it does not account for gradual uptake over time against a well-established comparator.”

6.56 The results of sensitivity analyses assessing a gradual increase in the market share of RIV4 are presented in Table 13. The ESC considered that the sensitivity analysis applying a gradual increase in market share to 50% by Year 3 was particularly informative.

**Table 13: Sensitivity analyses for RIV4 market share**

|  | Total over 6 years | % change |
|--|--------------------|----------|
| <b>Base case</b>   | <sup>1</sup>       | -        |
| Market share: Y1: 16.7%; Y2: 33.3%; Y3 to Y6: 50.0%.                           | <sup>1</sup>       | -16%     |
| Market share: Y1: 8.3%; Y2: 16.7%; Y3: 25.0%; Y4: 33.3%; Y5: 41.7%; Y6: 50.0%. | <sup>2</sup>       | -40%     |

Source: ATAGI post-submission advice, p5.

Abbreviations: Y, Year.

The redacted values correspond to the following ranges:

<sup>1</sup> \$40 million to < \$50 million

<sup>2</sup> \$20 million to < \$30 million

- 6.57 The submission assumed the influenza vaccine coverage rate (the uptake rate) would be 63.1% based on 2023 utilisation of influenza vaccines in Australians aged  $\geq 65$  years, sourced from the Australian Immunisation Register, reported by the National Centre for Immunisation Research and Surveillance. The submission noted there has been annual variation in this rate during recent years. The influenza vaccine coverage rate in persons aged  $\geq 65$  years was 61.9%, 64.9% and 70.0% in 2020, 2021 and 2022, respectively.<sup>2</sup> The ATAGI post-submission advice stated “ATAGI considered the assumption of stable vaccination rates over the next 6 years (remaining at the 2023 rate) was uncertain, but may be reasonable in the absence of any other data.”
- 6.58 There may be a small increase in utilisation due to uptake in individuals with egg allergies, although this is expected to be minor.

## 7 PBAC Outcome

- 7.1 The PBAC recommended that influenza vaccine (Flublok® Quadrivalent, RIV4) be a designated vaccine for the purposes of the *National Health Act 1953* for vaccination against influenza in people aged at least 65 years of age. The PBAC’s recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of RIV4 would be acceptable if it were cost-minimised against adjuvanted quadrivalent influenza vaccine (aQIV).
- 7.2 The PBAC noted that the consumer comments outlined that RIV4 would provide an additional option for influenza vaccination in people aged  $\geq 65$  years.
- 7.3 The PBAC considered that the comparator nominated by the submission, aQIV, was appropriate.
- 7.4 The PBAC noted that the submission did not identify any studies comparing RIV4 and aQIV, and instead presented studies comparing RIV4 and adjuvanted trivalent influenza vaccine (aTIV) on the basis that the PBAC had previously accepted that aQIV is at least non inferior to aTIV. No indirect comparisons were presented.
- 7.5 The PBAC noted that the key study presented, Izurieta 2021, was a retrospective analysis of US Medicare claims data with an uncertain risk of bias. Though the study attempted to minimise the risk of bias by using an inverse probability of treatment weighting (IPTW) approach, the PBAC considered that the potential for residual confounding due to unmeasured variables could not be excluded. The PBAC noted that, while Izurieta 2021 found RIV4 was associated with a statistically significant improvement in relative vaccine effectiveness (rVE) for the outcome of influenza inpatient stays versus aTIV (10.7%, 95% CI: 2.7%, 17.9%), there was no statistically significant difference in the primary outcome of influenza hospital encounters (5.6%, 95% CI: -0.6%, 11.4%). The PBAC noted that the ATAGI pre-submission advice stated

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<sup>2</sup> <https://ncirs.org.au/influenza-vaccination-coverage-data/historical-national-influenza-vaccination-coverage-2020-2022>. Accessed 17 November 2023.

“ATAGI had reasonable confidence that RIV4 is ‘at least’ equivalent to adjuvanted vaccines in this population, but was less confident that the available data were sufficient to support a claim of superiority”.

- 7.6 The PBAC noted that additional immunogenicity data was included in the PBAC submission which had not been included in the ATAGI pre-submission advice, with the ATAGI post-submission advice stating “Overall, the additional studies presented in the PBAC submission do not change ATAGI’s previous advice that RIV4 is ‘at least’ equivalent to adjuvant vaccines in individuals aged  $\geq 65$  years”.
- 7.7 The PBAC considered that the claim of “at least non-inferior” comparative effectiveness versus aQIV was reasonable.
- 7.8 The PBAC noted that RIV4 appeared to be associated with a similar incidence of adverse events one day after vaccination compared with aTIV, and the TGA Delegate had concluded: “The safety profile of RIV4 has been adequately characterised in adults. The exposure was adequate and there appears to be sufficient post-market experience.” Overall, the PBAC considered that the claim of “at least non-inferior” comparative safety versus aQIV was reasonable.
- 7.9 The PBAC noted that the submission requested a “technology premium” for RIV4 due to: potential advantages over alternative egg- and cell-based quadrivalent influenza vaccines; the potential benefits associated with the diversification of the vaccine manufacturing process; and to support investment in new vaccine technologies in Australia. The ATAGI pre-submission advice stated “it is plausible that RIV4 has some benefits over standard dose quadrivalent influenza vaccines given the higher HA dose as well as advantages over egg-based vaccines in terms of avoiding adaptations (primarily affecting the A/H3N2 strain) during the manufacturing process.” However, the PBAC noted that claimed advantages were not based on comparative clinical data and considered that the clinical relevance of any potential differences was unclear. The PBAC also noted no comparative evidence was available that suggested there would be any clinical benefit with RIV4 versus aQIV. The key study presented, Izurieta 2021, was a retrospective observational study with an uncertain risk of bias, however it did not demonstrate a statistically significant difference between RIV4 and aTIV for the primary outcome of influenza hospital encounters (5.6%, 95% CI: -0.6%, 11.4%).
- 7.10 Given it had considered that: the claim of “at least non-inferior” comparative effectiveness and safety versus aQIV was reasonable; the comparative clinical evidence provided did not demonstrate any clinical benefit, aQIV already has a premium over non adjuvant influenza vaccines, the PBAC considered that RIV4 should be cost-minimised against aQIV with no premium applied.
- 7.11 The PBAC considered that the equi-effective doses should be one dose of RIV4 0.5mL and one dose of aQIV 0.5mL.
- 7.12 The PBAC noted that, while the submission assumed that the market share of RIV4 would be 50% each year, the ATAGI post-submission advice stated the “assumption

of a peak uptake of 50% may be reasonable...However, the assumption that RIV4 will achieve peak uptake in the first year of listing was not reasonable as it does not account for gradual uptake over time against a well-established comparator.” The PBAC agreed with ATAGI and considered that the market share of RIV4 was likely to reach 50% by Year 3 (i.e., the PBAC considered the following market share assumptions were reasonable: 16.7% in Year 1, 33.3% in Year 2 and 50% in Years 3 to 6).

7.13 The PBAC considered that the other assumptions applied in the financial estimates were reasonable, but also noted the price of RIV4 would need to be updated to reflect its consideration that RIV4 should be cost-minimised against aQIV with no premium applied.

7.14 The PBAC noted that this submission is not eligible for an independent review as independent review is only relevant to requests for PBS listing.

**Outcome:**

Recommended

## 8 Recommended listing

8.1 Add new item to the Determination:

| Vaccine and the circumstances in which vaccine may be provided                            | Brand                 | Formulation       | Number and timing of doses |
|---|-----------------------|-------------------|----------------------------|
| Influenza Vaccine   | Flublok® Quadrivalent | Injection (0.5mL) | 1 dose per calendar year   |
| Circumstances<br>Vaccine may be provided:<br>to a person who is at least 65 years of age. |                       |                   |                            |

***This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.***

## 9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## 10 Sponsor’s Comment

The sponsor had no comment.