Adjuvanted Trivalent Influenza Vaccine; aTIV and Adjuvanted Quadrivalent Influenza Vaccine; aQIV (influenza vaccine, surface antigen, inactivated, adjuvanted with MF59C.1)

EU Risk Management Plan (EU-RMP)

Redacted

RMP version number:	3.0
Data lock point for this RMP:	15 March 2023
Date of final sign-off:	02 November 2023
Rationale for submitting an RMP:	Extension of the age indication for aQIV: Adults 50 years of age and older
Summary of significant changes in this RMP:	Extension of indication for aQIV: Prophylaxis of influenza in adults 50 years of age and older; Update in Part II, Module SI with new references; Update in Part II, Module SII with exposures from studies V200_10 and V118_23; Changes to Part III, Annex II and Annex III; Inclusion of studies V200_10 and V118_23 in Annex II. Removal of the integrated dataset analysis as an additional pharmacovigilance activity.
Other RMP versions under evaluation:	Not applicable
Details of the current approved RMP:	aTIV and aQIV EU-RMP: Version 2.0 aTIV approved with Mutual Recognition Procedure Date of approval: 10 January 2021 aQIV approved with Centralised Procedure Date of approval: 14 January 2021
Qualified Person for Pharmacovigilance (QPPV) name:	Juergen Zorn, MD
QPPV signature:	The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file .

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ABBREVIATIONS

ACIP	Advisory Committee on Immunisation Practices
ADR	Adverse Drug Reaction
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
(a)TIV	(Adjuvanted) Trivalent Influenza Vaccine
(a)QIV	(Adjuvanted) Quadrivalent Influenza Vaccine
CDC	Centre for Disease Control and Prevention
CSR	Clinical Study Report
CT	Clinical Trials
CTAB	Cetyltrimethylammonium bromide
COVID-19	Coronavirus Disease 2019
DRIVE	Development of Robust and Innovative Vaccine Effectiveness
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EMA	European Medicines Agency
EPSS	Enhanced Passive Safety Surveillance
ESS	Enhanced Safety Surveillance
GLP	Good Laboratory Practice
EU	European Union
GBS	Guillain-Barre Syndrome
GVP	Good Pharmacovigilance Practice(s)
HA	Haemagglutinin Antigen
HI	Haemagglutination Inhibition
ICSR	Individual Case Safety Report
IMI	Innovative Medicines Initiative
ITP	Immune Thrombocytopenia Purpura
INN	International Non-proprietary Name
NIVEL	Netherlands Institute for Health Services Research
NH	Northern Hemisphere
NHS	National Health Service
PSUR	Periodic Safety Update Report
PCV13	13-valent Pneumococcal Conjugate Vaccine
PPSV23	23-valent Pneumococcal Polysaccharide
rAEI	Reactogenic Adverse Event of Interest
RMP	Risk Management Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SH	Southern Hemisphere
SmPC	Summary of Product Characteristics
UK	United Kingdom
US	United States
VE	Vaccine Effectiveness
WHO	World Health Organization

PART I: PRODUCT(S) OVERVIEW

Active substance(s) (International Non-proprietary Name [INN] or common name)	Influenza vaccine, surface antigen, inactivated, adjuvanted with MF59C.1 Adjuvanted Trivalent Influenza Vaccine (aTIV) Adjuvanted Quadrivalent Influenza Vaccine (aQIV)
Pharmaco-therapeutic group (ATC Code)	Group: Influenza vaccine ATC Code: J07BB02
Marketing Authorisation Holder or Applicant	aTIV: Seqirus S.r.l. aQIV: Seqirus Netherlands B.V.
Number of medicinal products to which this RMP refers	Two
Invented name(s) in the European Economic Area (EEA)	aTIV: Fluad® aQIV: Fluad® Tetra
Marketing Authorisation procedure	aTIV: Mutual Recognition Procedure aQIV: Centralised procedure
Hyperlink to the Product Information	aTIV: SmPC aQIV: SmPC
Brief description of the product: chemical class	Adjuvanted Trivalent and Quadrivalent Influenza Vaccines (aTIV and aQIV) are surface antigen, inactivated, influenza virus vaccines adjuvanted with MF59C.1 for active immunisation against influenza. MF59C.1 is an oil-in-water emulsion, composed of squalene as the oil phase, stabilised with the surfactants polysorbate 80 and sorbitan trioleate, in citrate buffer.
Summary of mode of action	aTIV is supplied as 0.5 mL single dose pre-mixed syringe containing a sterile preparation of three purified inactivated influenza virus antigens in an isotonic buffer solution, combined with the MF59C.1 adjuvant, for intramuscular (IM) administration. aQIV is supplied as 0.5 mL single dose pre-mixed syringe containing a sterile preparation of four purified inactivated influenza virus antigens in an isotonic buffer solution, combined with the MF59C.1 adjuvant, for IM administration.

Important information about its composition (e.g., origin of active substance of biological, relevant adjuvants or residues for vaccines)	Haemagglutinin and neuraminidase antigens present in the vaccines induce a protective antibody response in vaccinated individuals within 2 to 3 weeks after immunisation. aTIV suspension includes antigens of three influenza virus strains; two type A strain subtypes (A/H3N2, A/H1N1) and one type B strain (from the B/Victoria or B/Yamagata strain lineages) as recommended by the World Health Organization (WHO) and the relevant National Control Authorities for the Southern Hemisphere or Northern Hemisphere. aQIV suspension includes antigens of four influenza virus strains; two type A strain subtypes (A/H3N2, A/H1N1) and two type B strains (one from the B/Victoria and one from the B/Yamagata influenza strain lineages) as recommended by WHO and the relevant National Control Authorities for the Southern Hemisphere or Northern Hemisphere. The surface antigens (haemagglutinin and neuraminidase) are obtained from the three (aTIV) or four (aQIV) influenza virus strains propagated in eggs, and then adjuvanted with MF59C.1. Each 0.5 mL dose contains 15 micrograms of haemagglutinin for each influenza virus strain. Excipients Redacted Sodium chloride Potassium chloride Potassium dihydrogen phosphate Disodium phosphate dihydrate Magnesium chloride hexahydrate Calcium chloride dihydrate Water for injections Redacted

<table>
<tr><td></td><td>Adjuvant
MF59C.1 is a proprietary adjuvant that is composed of the following:
<table><tr><th></th><th>Per 0.5 mL dose</th><th>Units</th></tr><tr><td>Squalene</td><td>9.75</td><td>milligrams</td></tr><tr><td>Polysorbate 80</td><td>1.175</td><td>milligrams</td></tr><tr><td>Sorbitan trioleate</td><td>1.175</td><td>milligrams</td></tr><tr><td>Sodium citrate</td><td>0.66</td><td>milligrams</td></tr><tr><td>Citric acid</td><td>0.04</td><td>milligrams</td></tr><tr><td>Water for injections</td><td>Up to 0.5</td><td>millilitres</td></tr></table>
Manufacturing Residuals
<table><tr><th></th><th>Per 0.5 mL dose</th><th>Units</th></tr><tr><td>Cetyltrimethylammonium bromide (CTAB)</td><td>≤12</td><td>micrograms</td></tr><tr><td>Ovalbumin</td><td><1</td><td>micrograms</td></tr><tr><td>Formaldehyde</td><td><1</td><td>micrograms</td></tr><tr><td>Hydrocortisone</td><td><0.005</td><td>nanograms</td></tr><tr><td>Kanamycin</td><td>≤0.06</td><td>micrograms</td></tr><tr><td>Neomycin</td><td>≤0.04</td><td>micrograms</td></tr></table></td></tr>
<tr><td>Indication(s) in the EEA
Current (if applicable)</td><td>Current:
aTIV: Prophylaxis of influenza in the elderly (65 years of age and older)
aQIV: Prophylaxis of influenza in adults (50 years of age and older).</td></tr>
<tr><td>Proposed (if applicable)</td><td>Proposed: N/A</td></tr>
<tr><td>Dosage in the EEA
Current (if applicable)</td><td>Current:
aTIV: Elderly (65 years of age and older): 0.5 mL (single dose), IM
aQIV: Adults (50 years of age and older): 0.5 mL (single dose), IM</td></tr>
<tr><td>Proposed (if applicable)</td><td>Proposed: N/A</td></tr>
<tr><td>Pharmaceutical form(s) and strengths
Current (if applicable)</td><td>Current:
aTIV
Suspension for injection (0.5 mL in pre-filled syringe): 15 micrograms haemagglutinin each of A/H3N2,</td></tr>
</table>

Proposed (if applicable)	A/H1N1 and one B (B/Victoria or B/Yamagata) strains per 0.5 mL dose <u>aQIV</u> Suspension for injection (0.5 mL in pre-filled syringe): 15 micrograms haemagglutinin each of A/H3N2, A/H1N1, B/Victoria and B/Yamagata strains per 0.5 mL dose
	Proposed: N/A
Is/will the product be subject to additional monitoring in the European Union (EU)?	aQIV is subjected to additional monitoring

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

Indications

Adjuvanted Trivalent Influenza Vaccine (aTIV) is indicated for prophylaxis of influenza in elderly of 65 years of age and older in the EEA.

Adjuvanted Quadrivalent Influenza Vaccine (aQIV) is indicated for prophylaxis of influenza in adults 50 years of age and older.

Influenza virus strains included in the aTIV vaccine are the A/H1N1, A/H3N2, and one type of B strain (B/Victoria or B/Yamagata).

Influenza virus strains included in the aQIV vaccine are the A/H1N1, A/H3N2, and B strains (B/Victoria and B/Yamagata).

Influenza infection

Influenza is an infectious acute respiratory disease of global importance caused by an influenza virus. In temperate climates, influenza generally affects persons from November to March in the Northern Hemisphere (NH) and from May to September in the Southern Hemisphere (SH). It can occur all year round in tropical climates. The virological basis for recurrent epidemics is

a continual process of small changes in influenza surface antigens to escape host immunity (antigenic drift). A/H3N2 viruses have the highest rate of evolution among the influenza subtypes currently circulating (Ferguson, Galvani & Bush, 2003), with antigenically distinct strains emerging on average every 2 to 5 years; Influenza B viruses have a lesser propensity for antigenic changes.

Influenza epidemiology

Influenza occurs in distinct outbreaks of varying extent every year. This epidemiologic pattern reflects the changing nature of the antigenic properties of influenza viruses, and their subsequent spread depends upon multiple factors, including transmissibility of the virus and the susceptibility of the population. All age groups are affected, though the proportions of the groups vary from year to year according to the dominating viruses and the level of population immunity. The annual burden of influenza thus also varies.

It remains difficult to assess the true burden of influenza in terms of incidence, deaths and hospitalisations because of the poor specificity of clinical diagnosis, and because influenza testing is not routinely sought (Poehling et al., 2006). There are no unique signs or symptoms of influenza, and many have considerable overlap in the clinical manifestations of other respiratory infections. In addition, diagnosis cannot be based on seasonality alone, because respiratory syncytial virus and other respiratory viruses can circulate concurrently with influenza virus (Iwane et al., 2004; Monto, Malosh & Petri, 2014; Szilagyi et al., 2016).

Overall, the World Health Organization (WHO) estimates that worldwide annual influenza epidemics result in about 3 to 5 million cases of severe illness, and about 290,000 to 650,000 respiratory deaths (WHO, 2022). In the EU/EEA region, seasonal influenza is estimated to cause 4 to 50 million symptomatic cases each year, and 15,000 to 70,000 European citizens die every year of causes associated with influenza (ECDC, 2019). Centre for Disease Control and Prevention (CDC) estimate that influenza has resulted in 9 million – 41 million illnesses, 140,000 – 710,000 hospitalisations and 12,000 – 52,000 deaths annually between 2010 and 2020 (CDC, 2022). Across age groups, the burden of influenza disproportionately falls on individuals <5 years of age and ≥65 years of age as further outlined in more detail below (Neuzil et al., 2000; Thompson et al., 2009; Rolfes et al., 2016).

During the Coronavirus disease 2019 (COVID-19) pandemic, there has been a 99% reduction in the diagnosis of influenza virus infection during the 2020/2021 and 2021/2022 seasons. From early 2020, during the influenza seasons in the SH and NH, global mortality rates from influenza fell to record low levels. In the United States (US), between October 2020, and July 2021, the CDC reported that out of 1.3 million laboratory tests, there were 2,136 positive test results for the influenza virus, and 748 reported deaths due to influenza. These findings were dramatic in contrast to surveillance data from the 2019/2020 influenza season that reported 38

million cases of influenza and 22,000 deaths due to influenza (Parums, 2021). However, after public health measures taken to minimise COVID-19 transmission, have been reduced, the number of influenza cases has started to increase in many countries in the NH 2022 influenza season. The co-circulation of influenza and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viruses raises the possibility of a more severe winter respiratory virus season (WHO, 2022).

Elderly population - epidemiology, morbidity, and mortality

The higher burden of influenza among older adults relative to younger adults is in part related to the age-related decline of the immune response (immunosenescence) (Lambert et al., 2012). This increases their susceptibility to influenza and risk of serious complications, leading to increased influenza related hospitalisations and deaths. Influenza morbidity and mortality in older adults vary with the circulating seasonal strains. Older adults are particularly impacted in seasons dominated by A/H3N2, a strain with the highest frequency of antigenic modifications and the highest probability of mismatch with influenza vaccine strain. Influenza-related hospitalisation rates for A/H3N2 infections were approximately 5 times higher in older adults as compared to the overall population (Zhou et al., 2012).

In the United Kingdom (UK), influenza-related hospitalisation rate was estimated to be 101/100,000 population for individuals 65 to 74 years of age, and 252/100,000 population for individuals ≥75 years of age relative to the overall rate of 49/100,000 population (Matias et al., 2016). In Norway, from 2008 to 2017, the average hospitalisation rate in the age groups ranged from 62 per 100,000 for those who were 60-69 years of age to 241 per 100,000 in the 80+ year age group (Hauge et al., 2019). In Spain between 2010-2011 to 2015-2016, relative to those 15-65 years of age, cumulative rates for ≥65 years of age were ~3 times higher for severe hospitalised confirmed influenza cases, ~2 times higher for intensive care unit admissions, and ~6 times higher for deaths in influenza hospitalised patients (Oliva et al., 2018).

While influenza seasons can vary in severity, during most seasons, people 65 years and older bear the greatest burden of severe disease. Approximately 90% of influenza-related deaths and 50-70% of influenza-related hospitalisations occur among people in this age group. The prevalence of chronic diseases changes with increasing age beyond 65 years, as does frailty and functional status. Because of their increased risk, older adults are a priority group for vaccination. (CDC, 2022).

Influenza also contributes substantially to the mortality rate among ≥65 years of age. In the WHO European Region, of the more than 44,000 deaths occurring annually (ranging between ~28,000 to ~70,000 deaths per season) from influenza related causes, approximately 75% of these deaths occur in individuals ≥65 years of age (Iuliano et al., 2018). In the US, approximately 34,200 deaths occurred from influenza-related causes in the 2018/2019 season

and 61,000 in the 2017/2018 season, with elderly accounted for 75-83% of these deaths (CDC 2020).

Adults 50-64 years old - epidemiology, morbidity, and mortality

There is also growing recognition of a high burden of influenza in adults 50-64 years of age. About one-fifth of the US population (approximately 63 million people) are aged between 50 and 64 years, and among these individuals, approximately one-third have an underlying medical condition that puts them at higher risk for influenza complications (CDC, 2019). In the US, the estimated rate of hospitalisations due to influenza disease is 3-fold higher in adults 50-64 years of age compared to the younger adult (18-49 years) age group (155.1 vs 48.4 per 100,000 population). Furthermore, the estimated number of medical visits due to influenza illnesses is higher in the 50-64 years age group (3.97 million) compared to older adults (1.72 million) (CDC, 2019).

The data from ten influenza seasons between 1996-2006 in five European countries (Netherlands, UK, France, Portugal, and Spain) show the percentage of all-cause mortality caused by influenza activity, in the age group 50-64 years old, ranged between 1.7-3.4% for the countries studied. The percentage of mortality due to respiratory disease caused by influenza activity was similar for the age groups 50-64 years (9.4-19.4%) and 65 years and older (9.4-19.3%). The percentage of mortality due to pneumonia and influenza caused by influenza activity was also similar for the age groups 50-64 years (11.8-24.5%) and 65 years and older (12.1-25.1%). The percentage of hospital admissions due to pneumonia and influenza ranged between 3.3-12.3% (NIVEL, 2010).

In the EU, seasonal influenza vaccine is also recommended for older adults 50-64 years old (EU Vaccination Information Portal, 2022). In 2010, the Advisory Committee on Immunisation Practices (ACIP) acknowledged a high burden of influenza disease in individuals 50-64 years of age and, consequently, defined the risk group for older adults as 50 years and older. In the UK in light of the risk of co-circulation of influenza and COVID-19, the 2020/2021 national influenza vaccination program has been extended to include adults 50-64 years of age for the 2020/2021, 2021/2022, and 2022/2023 influenza seasons (National Health Service [NHS] 2020; NHS 2021; NHS 2022). Vaccination has also been recommended for adults aged 50 years and older in Austria, for adults aged 55 years and older in Malta and Poland, and for adults aged 60 years and older in Germany, Greece, Hungary, Iceland, the Netherlands and Slovakia (ECDC 2022; Su et al. 2019).

Demographics of the Population and Risk Factors for the Disease

The CDC and European Centre for Disease Prevention and Control (ECDC) recommend annual seasonal influenza vaccination for the following risk groups: pregnant women at any

stage of pregnancy, children aged between 6 months to 5 years, elderly individuals (65 years and older), and individuals with chronic medical conditions (CDC, 2022, ECDC 2022). WHO additionally recommends vaccination for health-care workers (WHO, 2022). Additionally, ACIP recommends vaccination for persons aged 50-64 years because this group has an elevated prevalence of certain chronic medical conditions (CDC, 2022).

Main Existing Treatment Options

Seasonal influenza vaccination

Vaccination is the most effective form of influenza prevention. Injected inactivated influenza vaccines are the most common type of vaccine throughout the world. In 2011, a live attenuated influenza vaccine was also approved in the EU for children and adolescents. The main objective of seasonal influenza vaccination is to reduce the risk for those who would be predisposed to complications if they were to become infected.

In 2003, the World Health Assembly, which includes all EU/EEA countries, recommended targeting 50% of the elderly for vaccination uptake by 2006 and 75% by 2010. Moreover, an EU target was set by the Council of all EU ministers of health of achieving 75% vaccination coverage by 2014−15 in the older age groups, and if possible, extending this to people with chronic conditions (ECDC, 2022).

In the US, in the influenza 2021/2022 season, vaccination coverage with ≥1 dose of influenza vaccine was 57.8% among children 6 months through 17 years, and 49.4% amongst adults ≥18. Half of all people ≥6 months (51.4%) were vaccinated during the 2021–22 season. Coverage among adults in the US is nearly 20 percentage points lower than the Healthy People 2030 national target of 70% for influenza vaccination of persons ≥6 months; coverage among children is lagging by approximately 12 percentage points (CDC, 2022).

Personal protective measures

Apart from vaccination and antiviral treatment, public health management includes personal protective measures such as those set out below:

- Regular hand washing and proper drying of the hands. When handwashing is not possible, alcohol-based hand sanitizers are an option.
- Good respiratory hygiene and cough etiquette – covering the mouth and nose when coughing or sneezing, using tissues and disposing of them correctly, followed by proper hand hygiene after contact with respiratory secretions.
- Those who feel unwell, feverish or have other symptoms of influenza should self-isolate as soon as possible.

Other measures include:

- Avoiding close contact with sick people (e.g., by maintaining a distance of at least one metre from someone with symptoms of influenza and avoiding crowded situations). When distance cannot be maintained, reducing the time of close contact with people who might be ill may be an option.
- Avoiding touching one's eyes, nose, or mouth. Viruses may be spread when a person touches something that is contaminated with the virus and then touches his or her eyes, nose, or mouth (CDC, 2022; ECDC, 2022).

The recommendations for mask wearing have changed substantially during the COVID-19 pandemic, as this has been one of the most important measures for containing and reducing ongoing community transmission. A great deal of evidence has emerged since the beginning of the pandemic regarding the effectiveness of masks in reducing the spread of SARS-CoV-2. Since influenza follows the same transmission route as SARS-CoV-2, it is recommended to wear a mask in confined public spaces, such as shops, supermarkets, transportation hubs and when using public transport. Wearing a face mask should be considered in crowded outdoor settings where physical distancing is not possible. Moreover, face masks should be considered during the period when influenza and SARS-CoV-2 are co-circulating, especially for vulnerable categories, such as the elderly or those with underlying medical conditions (CDC, 2022; ECDC, 2022).

Symptomatic treatment

Most simple seasonal influenza cases are managed symptomatically, and patients are advised to stay at home and rest to minimise the risk of infecting others in the community. Treatment focuses on reducing fever and relieving the symptoms. An influenza diagnosis can be confirmed by submitting nasopharyngeal specimens for laboratory analysis. It is considered important that patients monitor themselves to detect whether their condition deteriorates, and they require medical intervention (ECDC, 2022).

Antivirals

Antiviral treatment is recommended as soon as possible for any patient with suspected or confirmed influenza who:

- is hospitalised;
- has severe, complicated, or progressive illness; or
- is at higher risk for influenza complications.

Decisions about starting antiviral treatment for patients with suspected influenza should not wait for laboratory confirmation of influenza virus infection. Empiric antiviral treatment should be started as soon as possible in the above priority groups (CDC, 2022).

For hospitalised patients with suspected or confirmed influenza, initiation of antiviral treatment with oral or enterically administered oseltamivir is recommended as soon as possible. For outpatients with complications or progressive disease and suspected or confirmed influenza (e.g., pneumonia, or exacerbation of underlying chronic medical conditions), initiation of antiviral treatment with oral oseltamivir is recommended as soon as possible. For outpatients with suspected or confirmed uncomplicated influenza, oral oseltamivir, inhaled zanamivir, intravenous peramivir, or oral baloxavir may be used for treatment, depending on the approved age groups and contraindications. In one randomised controlled trial, baloxavir had greater efficacy than oseltamivir in adolescents and adults with influenza B virus infection (CDC, 2022).

There are four antiviral drugs approved by the European Medicines Agency (EMA) available in the EU Member States to treat influenza. These includes oseltamivir, zanamivir, peramivir and baloxavir. For the best clinical benefit, treatment with antivirals should be given early in the infection, within 48 hours, (the earlier the better), to reduce the fever and flu-like symptoms. Antivirals may also reduce the risk of complications such as ear infections in children, respiratory complications requiring antibiotics, and hospitalisation in adults. However, at least one observational study of A(H1N1)pdm09 found improved survival in the severely ill when antiviral treatment was provided within five days of symptom onset (ECDC, 2022).

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

aTIV

Non-clinical studies performed with aTIV include assessment of immunogenicity (mice and rabbits), efficacy (mice), repeat dose toxicity (rabbits), reproductive and developmental toxicity (rabbits), and dermal sensitization (Guinea pigs). aTIV was immunogenic in mice and rabbits, and protected mice from challenge with influenza virus. No safety pharmacology studies were performed with aTIV.

In repeat-dose Good Laboratory Practice (GLP) toxicity studies in rabbits, the clinical dose of aTIV was administered as two or three 0.5 mL IM injections 14 days apart. aTIV was immunogenic, and no indication of local or systemic toxicity was observed.

A GLP study in female rabbits was performed to assess any effects on reproductive and developmental parameters. The clinical dose of aTIV was administered four times (twice

before mating and twice during gestation) by IM injection. aTIV was well-tolerated, did not cause maternal or embryofoetal toxicity, was not teratogenic, and had no effects on postnatal development. aTIV was immunogenic in maternal rabbits, developing foetuses had comparable titres, and antibodies persisted through the first four weeks of life in F1 kits.

aTIV did not cause hypersensitivity based on a GLP Guinea pig study. No additional non-clinical studies were warranted because no target organ or systemic toxicity was identified, and no adverse or irreversible reactions were observed in any of non-clinical studies.

aQIV

Non-clinical data with aTIV are applicable to aQIV.

The non-clinical safety of a formulation equivalent to aQIV (containing 60 µg Haemagglutinin Antigen (HA) + 0.25 mL MF59C.1) was evaluated in a GLP rabbit repeat dose toxicity study. A comparator group received aTIV (45 µg HA + 0.25 mL MF59C.1). There were no notable differences in local and systemic effects following administration of vaccine containing 45 µg HA compared to vaccine containing 60 µg HA. Both vaccines were immunogenic, and no evidence of local or systemic toxicity was observed.

In this study, the maximum clinical dose (60 µg HA + 0.25 mL MF59C.1) and the clinical route of administration (IM) were used. The safety of 3 doses administered 14 days apart was evaluated; this regimen exceeds the number of doses administered to adults 65 years of age and older.

The excipients or chemical substances used in the manufacturing process or in the final product did not raise concerns in relation to safety. No genotoxicity testing was performed.

Testing of MF59 adjuvant

MF59 adjuvant was extensively evaluated in non-clinical studies. In repeat-dose rabbit studies, clinical pathology findings of increased fibrinogen and minor inflammatory; and degenerative changes at the injection site were consistent with the effects of IM injections of an immunologically active material. These findings were reversible within days to 1 to 2 weeks and considered non adverse.

MF59 did not affect cardiovascular and neurological parameters after repeated administrations in dogs. MF59 was not genotoxic (Ames test) or clastogenic (mouse micronucleus), was not a dermal sensitizer (Guinea pig), and was not teratogenic (rat and rabbit) or a developmental toxicant (rat).

Findings attributable to adjuvant were considered non adverse with antigens combined with MF59 or MF59 alone. In general, although immunogenicity is enhanced, toxicology related findings with MF59-adjuvanted vaccines were comparable to findings with MF59 alone.

Conclusion on non-clinical data

In non-clinical studies, MF59 adjuvanted influenza vaccine formulations were well tolerated and did not elicit local or systemic toxicity. There were no findings identified during non-clinical testing that warrant inclusion in the summary of safety concerns. No additional non-clinical studies were needed; the completed programme supports the licensed indications.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

aTIV:

Overall, 28,559 subjects received aTIV in Seqirus-sponsored investigational clinical trials (CTs) cumulatively until the data lock point (DLP) of 15 Mar 2023 (Table SIII.1). This number reflects cumulatively all subjects who have been exposed to all formulations of aTIV, i.e. including exposure to formulations with trace-thiomersal and with full thiomersal – both of which have been discontinued since 2003.

Table SIII.1 Cumulative subject exposure to aTIV in clinical trials

Exposure in completed studies*	Number of subjects
aTIV	**28,559**

*Estimates of cumulative subject exposure based upon actual exposure or randomised data from completed CTs. Data from completed trials as of 15 Mar 2023.

Note: If a subject participated in extension study(ies), then (s)he was counted only once.

The age and gender distributions of subjects treated with aTIV in completed CTs are summarised in Table SIII.2

Table SIII.2 Cumulative subject exposure to aTIV from completed clinical trials by age and gender

Sex	Number of subjects
Male	13,707
Female	14,852
Age group (years)	
≥6 months to <6 years	6,397
≥6 years to ≤18 years	414

>18years to <65 years	3,954
≥65 years	17,794

Cumulative exposure to aTIV by subject's ethnic origin treated in completed investigational trials are provided in Table SIII.3.

Table SIII.3 Cumulative subject exposure to aTIV from completed clinical trials by racial group

Racial group	Number of subjects
American Indian/Alaska Native/Pacific Islanders/Native Hawaiian	3
Asian	4,233
Black/African American	683
White	13,956
Other	247
Not Available	9,437
Total	**28,559**

Estimates of the cumulative subject exposure by number of doses received in completed trials are summarised in Table SIII.4

Table SIII.4 Cumulative subject exposure to aTIV from completed clinical trials by vaccine dose

Number of vaccine doses	Number of subjects
At least one dose	28,559
At least two doses	8,803
At least three doses	243
Total	**28,559**

aQIV

Overall 11,152 subjects received aQIV in seven completed Seqirus-sponsored investigational CTs (Studies V118_05, V118_05E1, V118_05E3, V118_20, V118_18, V118_23 and V200_10) cumulatively from aQIV Development International Birth Date (DIBD) of 17 Sep 2013 until the DLP of 15 Mar 2023 (Table SIII.5).

Table SIII.5 Cumulative subject exposure to aQIV in completed clinical trials

Vaccination	Number of subjects
aQIV	**11,152**

The age and gender distributions of subjects treated in completed investigational trials are summarised in Table SIII.6 and SIII.7.

Table SIII.6 Cumulative subject exposure to aQIV from completed clinical trials by gender

Sex	Number of Subjects
Male	4,989
Female	6,163
TOTAL	**11,152**

Table SIII. 7 Cumulative subject exposure to aQIV from completed clinical trials by age group

Age group	
6 to <84 months	5,741
50 to <65 years	1,083
≥65 years	4,328
TOTAL	**11,152**

Cumulative exposure to aQIV by subject's ethnic origin treated in completed investigational trials is provided in Table SIII. 8.

Table SIII. 8 Cumulative subject exposure to aQIV from completed clinical trials by racial group

Racial Group	Number of subjects*
American Indian/Alaska Native	79
Asian	3,858
Black/African American	822
Native Hawaiian/Pacific Islander	16
White	5,708
Other	669
Total	**11,152**

Cumulative exposure to aQIV by vaccination dose in completed investigational trials is provided in Table SIII.9.

Table SIII. 9 Cumulative subject exposure to aQIV from completed clinical trials by vaccine dose

Number of vaccine doses	Number of subjects
At least one dose	11,152
At least two doses	3,653
At least three doses	524
Total	**11,152**

Exposure by dose and by age groups in key paediatric clinical trials

Tables SIII.10 provides an overview on the total number of subjects exposed from all completed sponsored clinical studies of aQIV in the paediatric age group.

Table SIII. 10 Vaccine Exposure by number of doses (paediatric subjects ≥6 months to <6 years at first vaccination)

No. of subjects with Vaccine Exposure of at least:		
One dose	**Two doses**	**Three doses**
5,741	3,969	524

Source Table 101 CSR V118_05 (14.1.1.1.10, 14.1.1.1.11 and 14.1.1.13.1), Table 8 of V118_05E1 CSR, Table 9 of V118_05E3 CSR.
CSR: Clinical Study Report

Detailed exposure data by age group and dose volume have been derived from the parent study V118_05 only (i.e. the first annual vaccination) and is presented in Table Table SIII. **11**.

Table SIII. 11 Vaccine Exposure by dose regimen and paediatric age group (paediatric subjects ≥ 6 months to < 6 years; first annual vaccination)

No. of subjects with Vaccine Exposure of at least:		
Age group	**One dose**	**Two doses**
≥6 to < 24 months	1,319	1,110
≥24 to < 72 months	4,020	2,350
TOTAL	**5,339**	**3,460**

Source Table 101 Clinical Study Report V118_05 (14.1.1.1.10, 14.1.1.1.11 and 14.1.1.13.1)
Revaccination studies V118_05E1 and V118_05E3 have not been included in this table

Ongoing studies

There are no ongoing clinical studies with aQIV or aTIV.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

For aTIV and aQIV the populations not studied in CTs were those excluded according to eligibility criteria defined for the studies.

aTIV studies have not included subjects <6 months of age.

aQIV studies have not included subjects <6 months of age, and subjects >6 years to <50 years of age at the date of primary vaccination.

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

For both aTIV and aQIV, the main exclusion criteria were subjects with hypersensitivity to any component of the vaccine and conditions that are likely to compromise the safety of the subject (e.g. subjects with bleeding disorders) or condition that may compromise evaluation of vaccine-induced immune responses (medical conditions or medications/treatments that may cause immune suppression).

Except for subjects with hypersensitivity to vaccine components, the other conditions are not considered contraindications to vaccination (see Table SIV.1 and Table SIV.2).

Table SIV.1 Exclusion criterion, which will remain as contraindications for aTIV and aQIV

Criteria	Implications for target population
Hypersensitivity to the active substances, components of the adjuvant, excipients, residues	Persons with hypersensitivity must use alternative methods of prevention

Table SIV.2 Exclusion criteria which will not remain as contraindications for aTIV and aQIV

Criteria	Reason for being an exclusion criterion	Justification for not being a contraindication
Bleeding disorder	Safety of subjects	Benefit-risk is positive in this population with adequate warnings in the prescribing information
History of Guillain-Barre syndrome (GBS)	Potential confounder	Evidence for a causal relationship of GBS with other influenza vaccines is inconclusive; if an excess risk exists, it is probably slightly more than 1 additional case per 1 million persons vaccinated

Criteria	Reason for being an exclusion criterion	Justification for not being a contraindication
History of convulsions	Potential confounder	Overall risk is low, a history of convulsions is not a risk factor (see Part II Module SVII.3).
Immunocompromised	May have impaired response	Benefit-risk is positive in this population with adequate warnings in the prescribing information
Impaired mental status	Subjects cannot provide informed consent for clinical trial	Not applicable for marketed product as this is specific to consent for clinical trial participation

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The aTIV and aQIV clinical trial development programmes are unlikely to detect certain types of rare adverse drug reactions (ADRs), adverse reactions with a long latency, or those caused by prolonged or cumulative exposure (see Table SIV.3).

Table SIV.3 Limitations of adverse reaction detection common to clinical trial development programmes for aTIV and aQIV

Ability to detect adverse reactions	Limitation of trial programme		Discussion of implications for target population
	aTIV	aQIV	
Which are rare	28,559* subjects exposed to aTIV (all former and current formulations)	11,152** subjects exposed to aQIV	The clinical database is able to detect rare ADRs (those with a frequency between 1:1,000 to 1:10,000) if there were no background incidence (EMA/CHMP/VWP/457259/2014)
Due to prolonged exposure	Not applicable as this is a vaccine to be administered each influenza season		Not applicable as this is a vaccine to be administered each influenza season
Due to cumulative effects	8,803 subjects were revaccinated with aTIV once and 243 subjects were revaccinated twice***	3,969 subjects were revaccinated with aQIV in paediatric studies once and 524 twice****. Revaccination with aQIV has not been studied in adult subjects	The clinical database did not reveal a specific signal associated with revaccination. The revaccination clinical database is large enough to detect common ADRs (1:10 to 1:100)

Ability to detect adverse reactions	Limitation of trial programme		Discussion of implications for target population
	aTIV	aQIV	
Which have a long latency	Majority aTIV studies had a maximum 12 months of safety follow up; aQIV studies had 6 to 12 months of safety follow up.		Not applicable as vaccination (priming or seasonal revaccination) is conducted annually, so the period of 6 to 12 months safety follow-up is appropriate for this dosing frequency for longer latency adverse reactions

*Figure from Table SIII.1
** Figure from Table SIII.5
***Figure from Table SIII.4
**** Figure from Table SIII. 10

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.4 outlines exposure estimates of populations under-represented in the pivotal clinical trials, and whether they are contraindicated populations.

Table SIV.4 Limitations in respect to under-represented populations in clinical development programmes for aTIV and aQIV

Type of special population	Exposure
Pregnant and Breastfeeding women	These special populations are not applicable to aTIV and aQIV. The current indication does not include women of child-bearing potential due to the age of the target population.
Patients with hepatic or renal impairment	Studies V118_18 and V118_20 in elderly subjects with aQIV were open to community dwelling elderly either healthy or with comorbid conditions, so some subjects with these co-morbid conditions were enrolled. In studies V118_18 and V118_20, the proportion of subjects with hepatobiliary disorders were 6.1% and 5.8%, and the proportion of subjects with chronic kidney disease/ renal impairment or failure were 2.3% and 2.0%, respectively. Although there are limited clinical data in these populations from the aQIV clinical trial development programme, post marketing experience with aTIV and data from the worldwide literature have not identified any specific safety concerns. Patients with hepatic or renal impairment are considered more at risk of complications from influenza and are therefore targeted for

	vaccination via public health campaigns. Specific exposure estimates for subjects with hepatic and renal disorders not meeting criteria for clinical significance enrolled in the studies, were not systematically recorded. There is no contraindication for subjects with these conditions for aTIV and aQIV.
Patients with other significant, or clinically uncontrolled co-morbidity	Subjects with hypersensitivity to vaccine components, bleeding disorders, immunocompromising conditions, immunodeficiencies, and those with impaired mental capacity have been excluded from the aTIV and aQIV clinical trials. Although there is a lack of clinical data in these patient populations from the aTIV and aQIV clinical trial development programmes, post marketing experience with aTIV and data from the worldwide literature have not identified any specific safety concerns. aTIV has been open to community dwelling elderly likely to have various underlying conditions (also known as comorbidities) including cardiovascular disease, pulmonary disease, diabetes and other conditions common to this age group. In fact, study V70_27 encouraged enrolment of subjects with cardiovascular disease, pulmonary disease, metabolic (e.g., diabetes mellitus) and neurologic diseases, hepatic disease and renal disease. Similarly, aQIV clinical studies have been inclusive of subjects with comorbidities that pose a high risk for influenza complications, such as: • Asthma (regardless of severity) • Neurological conditions (such as cerebrovascular accident, including ischemic stroke, and dementia) • Chronic lung disease (such as chronic obstructive pulmonary disease) • Heart disease (such as coronary artery disease and congestive heart failure) • Blood disorders (such as anaemia) • Endocrine disorders (such as diabetes mellitus) • Kidney disorders • Liver disorders (such hepatic cirrhosis) • Metabolic disorders and nutritional deficiency • Weakened immune system due to disease or medication (such as people with HIV or AIDS, or cancer, or those on chronic steroids) • Receipt of long-term aspirin therapy

	• Morbidly obese In studies V118_18 and V118_20, prior to study enrolment, demographic data was collected from the subjects, including age, sex, race, ethnicity, height and weight, prior influenza vaccination, comorbidity, and the risk of complications from influenza indicated by a calculated score known as the comorbidity risk score (Hak et al., 2004). This risk assessment score incorporates medical comorbidity among other baseline characteristics and is a validated predictor of risk of complications from influenza in subjects ≥65 years of age. Using this model, a score of <50 is considered low risk and a score of ≥ 50 is considered high risk for hospitalisation due to pneumonia or influenza and death from any cause. In study V118_20, at study entry, scores <50 and ≥50 were observed in the per protocol analysis set for n=568/872 aQIV subjects (65.1%) and n=304/872 aQIV subjects (34.9%), respectively. In study V118_18, 2397/3291 aQIV subjects (72.8%) had a comorbidity score of <50 and 894/3291 subjects (27.2%) had a comorbidity score ≥50. In study V118_23, 912/1027 aQIV subjects (88.8%) had a comorbidity score of <50 and 115/1027 subjects (11.2%) had a comorbidity score ≥50. In V118_23 the subgroup of subjects with high comorbidity score was observed to have a higher immune response for H1N1, H3N2 and B Yamagata compared to the controls who received non-adjuvanted influenza vaccine. For both studies, at postvaccination, similar proportion of subjects of high risk and low risk of influenza complications achieved Haemagglutination inhibition (HI) titre ≥1:40. A trend to a lower seroconversion rate was seen in the high-risk group compared to the low risk group. A trend to a lower Geometric Mean Ratio was observed in the high-risk group compared to the low risk group for all influenza strains for aQIV. Though the immune response to aTIV or aQIV may be reduced in immunocompromised persons, including those receiving immunosuppressive therapy, this patient population is considered more at risk of complications from influenza and is therefore targeted for vaccination via public health campaigns.
Patients with a disease severity different from the inclusion criteria in the clinical trial population	Not applicable to aTIV and aQIV, as the subjects included in clinical trials were given influenza vaccine prophylactically and represent the indicated population.

Sub-populations carrying known and relevant polymorphisms	Not applicable to aTIV and aQIV.
Children	Clinical trials (including extension/revaccination trials) have been conducted in children 6 months to less than 17 years of age for aTIV and children 6 months to less than 7 years of age for aQIV. Fluad and Fluad Tetra are not currently approved in the paediatric age group in the EU. Pre-term newborns: No studies conducted to date Newborn infants (birth to 27 days): No studies conducted to date Infants and toddlers (28 days to 23 months): Clinical trials have been conducted in infants beginning at 6 months of age for aTIV and aQIV Children (2 years to 11 years): Clinical trials have been conducted in children to less than 7 years for aQIV and less than 11 years old for aTIV Adolescents (12 years to 17 years): No studies conducted to date for aQIV. For aTIV clinical trials have been conducted in this age group. Exposure estimates from clinical studies by paediatric age groups are summarised in Table SIII.2 and Table SIII.6.
Adults 50 years of age and older	The current approved age group for aTIV is for elderly ≥65 years of age. The current approved age group for aQIV is for adults 50 years of age and older. In V118_20, the total number of subjects included in the safety analysis was 888 aQIV subjects, of which there were 611 subjects in age group ≥65 to 74 years (69%); 246 subjects in age group ≥75 to 84 years (27%), and 31 subjects in age group ≥85 years (3%). In V118_18, the total number of subjects included in the safety analysis was 3,380 aQIV subjects, of which there were 2,405 in the 65 to 74 years age group (71.2%), 890 in the 75 to 84 years age group (26.3%), and 85 in the ≥85 years age group (2.5%). In V118_23, the total number of subjects included in the safety analysis was 1,027 aQIV subjects, of which there were 609 in the 50 to 59 years age group (57.1%) and 418 in the 60 to 64 years age group (40.7%).

	A broad age spectrum of subjects over the age of 50 years participated in aQIV trials and therefore, no limitations related to adults 50 years and older have been identified.
Patients of different racial and/or ethnic origin	Not applicable to aTIV and aQIV. There were no restrictions on enrolment of subjects by racial and/or ethnic origin in aTIV and aQIV clinical development. Exposure estimates from clinical studies by subject race across all age groups are summarised in Table SIII.3 and **Error! Reference source not found.**. Most subjects in the aTIV and aQIV exposure dataset were of White, Asian or Black/African American race.

SIV.4 Conclusions on the populations not-studied and other limitations of the clinical trial development programme

Missing information for aTIV and aQIV.

The main category of co-morbid conditions for which there is missing information are persons with abnormal function of the immune system, either due to clinical conditions affecting the immune system or through immune suppressive medications. However, it is known through clinical research with influenza vaccines in general and the way that vaccines mediate their effect, that persons with abnormal immune function are likely to have reduced immune responses to vaccination. This is not proposed to be listed as missing information in the elderly population.

Table SIV.5 Safety concerns due to limitations of the clinical trial programme

Safety concern	Comment	Outstanding concern?
None		

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

aTIV

A single 0.5 mL dose administered once yearly in elderly (65 years of age and older). The estimated exposure is based on the calculation that most individuals vaccinated with aTIV have

received one dose, except for paediatric population in Canada, where the estimate is two doses (0.25mL) per individual. The cumulative sales data excluding paediatric doses is unavailable.

aQIV

A single 0.5 mL dose administered once yearly in adults (50 years of age and older). The estimated exposure is based on the calculation that most individuals vaccinated with aQIV have received one dose.

SV.1.2 Exposure

aTIV

The cumulative patient exposure since the IBD of aTIV is estimated to be 191,311,302 doses, or approximately 191 million individuals (including paediatric exposure in Canada).

aQIV

Redacted The cumulative patient exposure from the IBD to the DLP is estimated to be 98,943,336 doses or approximately 99 million individuals.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 Potential for misuse for illegal purposes

Not applicable to influenza vaccines.

SVI.2 Conclusions

Safety concern	Comment	Outstanding concern?
None		

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Local (injection site) reactions including injection site erythema, injection site induration, injection site pain/tenderness, and injection site ecchymosis,
- Generalised skin reactions including pruritis, urticarial and non-specific rash,
- Systemic reactions including loss of appetite, nausea, vomiting, fatigue, myalgia, arthralgia, headache, chills, diarrhoea and fever (≥38°C).

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- Paraesthesia
- Extensive swelling of injected limb

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers:

- Anaphylaxis

Class effects for influenza vaccines:

- Neuritis,
- Encephalitis,
- Vasculitis,
- GBS,
- Demyelination,
- Bell's palsy,
- Haemolytic anaemia
- Immune thrombocytopenia purpura (ITP)

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

There are no important identified or important potential risks for aTIV and aQIV.

SVII.2 Reclassification of safety concerns with a submission of an updated RMP

This RMP for aTIV and aQIV includes paediatric and adults (50 year of age and older) clinical trial data, but the approved indication for aTIV and aQIV in the EEA is only for the elderly population. The proposed indication for aQIV is adults 50 years of age and older.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

There are no important identified risks or important potential risks for aTIV and aQIV.

SVII.3.2 Presentation of the missing information

Section SIV.4 discusses the populations not studied and other limitations of the clinical trial development programme and presents a summary of categories of missing information based on exclusion criteria from the aTIV and aQIV clinical development programme, and whether the excluded groups indicate a safety concern. There is no missing information for adults 50 years and older population.

SVII.4 Identified and potential interactions

SVII.4.1 Overview of potential for interactions

There are no studies investigating the potential interaction between aTIV and aQIV and other vaccines.

Data from two studies on the concomitant administration of aTIV with an approved 13-valent pneumococcal conjugate vaccine (PCV13) and an approved 23-valent pneumococcal polysaccharide vaccine (PPSV23) in an elderly population are available (Song et al., 2017, Song et al., 2015). These studies did not demonstrate that co-administration of aTIV with either PCV-13 or PPSV23 resulted in significant interference in antibody response. Although concomitant vaccination induced more frequent local pain, most of the local adverse reactions were mild. Systemic adverse reactions were generally mild, and no serious vaccine-related adverse events (AEs) occurred.

If aTIV or aQIV is to be given at the same time as other injectable vaccines, the vaccines should be administered at different injection sites. It should be noted that the adverse reactions may be intensified.

Immunosuppressive therapies may reduce the immune response to aTIV and aQIV.

There are limited clinical data on concomitant use of aTIV and aQIV with other medicines.

SVII.4.2 Important interactions

There are no important identified or important potential interactions.

SVII.5. Pharmacological class effects

SVII.5.1 Important pharmacological class effects

There are no important pharmacological effects relevant to aTIV in the elderly population and in aQIV in adults 50 years of age and older.

SVII.5.2 Important pharmacological class effects not discussed above

There are no important pharmacological class effects relevant to aTIV in the elderly population and in aQIV in adults 50 years of age and older.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1 Summary of Safety Concerns for aTIV and aQIV

Important identified risks	None
Important potential risks	None
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine PV activities for Seqirus products comply with Good Pharmacovigilance Practices (GVP) and fulfil the legal requirements per Directive 2001/83/EC and Regulation (EC) No. 726/2004. This includes all risks, whether potential or identified; routine PV includes management of Individual Case Safety Reports (ICSRs), Periodic Safety Update Reports (PSURs), monitoring safety profiles, and safety signal detection and evaluation.

Other forms of routine PV activities for adverse events following immunisation:

The "Interim guidance on Enhanced Safety Surveillance for seasonal influenza vaccines in the EU" (EMA/PRAC/222346/2014) requires the implementation of annual Enhanced Safety Surveillance (ESS) for influenza vaccines. Seqirus implemented Enhanced Passive Safety Surveillance (EPSS) for aTIV and intends to implement EPSS for aQIV (after product is marketed in the EU) during the Northern Hemisphere influenza season(s). The passive approach of the ESS is a routine pharmacovigilance activity and in accordance with chapter "V.B.9.1. RMP part III section Routine pharmacovigilance activities" of the GVP Module V.

EPSS is performed in the EU in the health care practice setting where aTIV or aQIV are planned to be administered as part of routine care among adults 50 years and older (aQIV) and elderly persons of 65 years and older (aTIV). The start of surveillance is aimed to start mid-September or with the start of seasonal influenza vaccination by the participating sites with aTIV or aQIV, whichever comes later. Up to 1,000 vaccine exposures are planned to be captured. The surveillance will continue until one week after the pre-specified 1,000 recorded vaccine administrations is reached and includes spontaneous AEs reported up to one week later.

Spontaneous AEs are analysed weekly as well as cumulatively at the end of the surveillance period for the purposes of signal detection. The weekly reviews are performed in order to monitor any potential change in reactogenicity given the current knowledge of the vaccine on an ongoing basis. The observed reporting rates for reactogenic AEs of interest (rAEIs) from the current season are evaluated in the context of the expected rates, where applicable and/or available using the most current summary of product information. All potential safety signals generated from this analysis will be handled as per the Seqirus signal detection processes. Full results will also be included in the PSUR. The trigger for submitting an expedited safety surveillance report will be the discovery of a potential signal.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Required additional PV activities

Not applicable.

Additional PV activities not required by regulators

As per the Guideline on Influenza vaccines Non-Clinical and Clinical Module (EMA/CHMP/VWP 457259/2014) of July 2016, other pharmacovigilance activities should include the estimation of aQIV vaccine effectiveness. This is currently achieved through a supporting Innovative Medicines Initiative (IMI) programme called DRIVE (Development of Robust and Innovative Vaccine Effectiveness).

- DRIVE (Development of Robust and Innovative Vaccine Effectiveness)

DRIVE initiative has been launched in July 2017. GSK, Sanofi Pasteur, Abbott and Seqirus, as vaccine manufacturers with marketed influenza vaccines in Europe, contributed to the genesis of the project. This project is a unique public-private partnership involving in addition to manufacturers, 11 partners including academic and public health institutes. DRIVE aims to assess the feasibility of building a sustainable platform in Europe able to generate brand specific influenza vaccine effectiveness data in Europe. As per the IMI legal framework, this is a 5 year partnership project, encompassing at least 4 consecutive influenza seasons. Studies

are intended to be conducted annually in European sites and the data generated will be pooled across participating centres, with the first pilot seasonal studies initiated during the 2017-2018 northern hemisphere influenza season.

Each year a report will be generated to synthesize data on influenza vaccine effectiveness collected across participating sites including data generated from the public health surveillances contributing to DRIVE. Results will be provided every year but will not trigger an RMP update unless the results impact public health or alter the benefit-risk profile of Seqirus vaccines, as per EMA agreement on 30th of April 2019 (EMA/248552/2019 Vaccine Working Party). Seqirus will not be the study sponsor or owner of the data, and will not control the scientific deliverables, which include the Study Protocol, Statistical Analysis Plan and Study Reports. Timelines are driven by the overall project and conditioned notably by logistics associated with 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 its marketed influenza vaccines in Europe.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table Part III.3.1 Summary table of additional PV activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Additional pharmacovigilance activities not required by regulators				
DRIVE analysis - A non-interventional study of vaccine effectiveness in the EU; seasonal influenza vaccine (aQIV) versus no vaccination in elderly ≥ 65 years (DRIVE analysis).	To perform an analysis of influenza vaccine effectiveness of aQIV vaccination versus no vaccination in elderly ≥ 65 years	Measure of vaccine effectiveness in routine care.	Planned for the initial influenza season of launch and annually thereafter.	Annual submission of results planned in December

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

This section contains components of the Risk Minimisation Plan.

V.1 ROUTINE RISK MINIMISATION MEASURES

Table V.1.1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
None	Not applicable

V.2 ADDITIONAL RISK MINIMISATION MEASURES

Routine risk minimisation activities as described in Section V.1 are sufficient to manage the safety concerns for aTIV and aQIV. Additional risk minimisation measures are not necessary, as there are no important identified and potential risks or missing information to be addressed.

V.3 SUMMARY OF RISK MINIMISATION MEASURES

Table V.3.1 Summary table of PV activities and risk minimisation activities by safety concern and population

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
None		
Important potential risks		
None		
Missing information		
None		

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR FLUAD (ATIV) AND FLUAD TETRA (AQIV)

Summary of risk management plan for Fluad (aTIV)

This is a summary of the risk management plan (RMP) for Fluad. The RMP details important risks of Fluad and how these risks can be minimised and how more information will be obtained about the Fluad risks and uncertainties (missing information).

Fluad summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Fluad should be used.

Important new concerns or changes to the current ones will be included in updates of the Fluad RMP.

I. The medicine and what it is used for

Fluad is authorised for prophylaxis of influenza in the elderly (65 years of age and older). It contains a purified, inactivated, surface antigen trivalent influenza vaccine, adjuvanted with MF59C.1. It is to be administered as a single 0.5 mL dose by intramuscular injection into the deltoid muscle.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Fluad, together with measures to minimise such risks, are outlined below:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

II.A List of important risks and missing information

Important risks of Fluad are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered.

Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Fluad. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine)

Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

Not applicable

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation.

II.C.2 Other studies in post-authorisation development plan

Not applicable

Summary of risk management plan for Fluad Tetra (aQIV)

This is a summary of the risk management plan (RMP) for Fluad Tetra. The RMP details important risks of Fluad Tetra and how these risks can be minimised and how more information will be obtained about Fluad Tetra risks and uncertainties (missing information).

Fluad Tetra summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Fluad Tetra should be used.

This summary of the RMP for Fluad Tetra should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of the Fluad Tetra RMP.

I. The medicine and what it is used for

Fluad Tetra is authorised for prophylaxis of influenza in adults 50 years of age and older. It contains purified, inactivated, surface antigen quadrivalent influenza vaccine, adjuvanted with MF59C.1. It is to be administered as a single 0.5 mL dose by intramuscular injection into the deltoid muscle.

Further information about the evaluation of Fluad Tetra benefits can be found in Fluad Tetra EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/fluad-tetra

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Fluad Tetra, together with measures to minimise such risks, are outlined below:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

II.A List of important risks and missing information

Important risks of Fluad Tetra are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered.

Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Fluad Tetra. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

Not applicable

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation.

II.C.2 Other studies in post-authorisation development plan

Not applicable

ANNEX 4 - SPECIFIC ADVERSE EVENT FOLLOW-UP FORMS

Not applicable.

ANNEX 6 - DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION MEASURES (IF APPLICABLE)

Not applicable.