2 Elements for a public summary

2.1 What is Influenza?

Influenza, also called flu, is an extremely common and contagious disease caused by a virus - *Myxovirus influenzae*. Uncomplicated infection is usually accompanied by the abrupt onset of fever (sometimes as high as 39°C to 40°C), and by some or all of the following: fatigue, headache, cough, muscle and joint pain, chills and runny nose.

Flu occurs in people of all ages, even healthy people. Flu is not usually a harmful disease but it can cause severe illness especially in the elderly, pregnant women, young children aged less than 2 years, and people with certain chronic diseases such as asthma, chronic bronchitis or heart disease, whatever their age, because these groups of people are at greater risk of complications such as pneumonia, life-threatening conditions and even death. However, even in healthy people, influenza may cause considerable illness, for example when a new influenza virus emerges that is highly infective. In addition, the negative impact of the disease is high when taking into consideration sick leave, family disturbances, loss of productivity, and health care costs.

2.2 Summary of treatment benefits

Annual influenza vaccination is the most effective method for preventing seasonal flu and its complications. Antiviral drugs and treatments for the flu symptoms such as painkillers and fever medications may also be used to treat flu once you are sick (ask your doctor for advice).

After vaccination, protection against flu generally lasts 6 to 12 months, depending on your body's response to the vaccine.

Because the two types of influenza virus (type A virus and type B virus) responsible for flu can change from year to year, the composition of the vaccine has also to be updated every year. This is why every year experts from, or collaborating with, the World Health Organization (WHO) meet and propose recommendations for the influenza virus strains to be used in the composition of the next season's vaccine.

Historically influenza vaccines have been trivalent, which means that they contain three (tri-) different inactivated influenza viruses to provide protection against flu: two influenza A virus subtypes and one influenza B virus. Vaxigrip® is such a trivalent vaccine.
Since 2001, two different lineages (families) of type B viruses have appeared and co-circulated. Therefore in order to increase protection against flu due to the type B viruses, Sanofi Pasteur has developed a quadrivalent influenza vaccine which contains four (quadri-) different inactivated influenza viruses: two influenza A virus subtypes and both influenza B lineages (families). QIV is such a quadrivalent vaccine.

2.3 Unknowns relating to treatment benefits

There is continuous need of recent and accurate information on the protective effects of influenza vaccine in the populations that are eligible to receive this vaccine.

Since the severity of the flu outbreak and the composition of the flu vaccine may vary from year to year, it is important to evaluate protective effects of the vaccine continuously.

To assess the protective effect of influenza vaccines in routine use in general populations and those populations considered specifically at risk to suffer from influenza-related illness,, Sanofi Pasteur has fostered the development of a Global Influenza Hospital Surveillance Network in several countries worldwide (Spain, China, Turkey, Brazil, the Czech Republic and the Russian Federation). This program aims to document the burden of severe influenza (leading to hospitalization) and to estimate the protective effects of influenza vaccine (vaccine effectiveness against severe influenza. Sanofi Pasteur and Sanofi Pasteur MSD are also involved in a collaborative European operational research project between several vaccine manufacturers focusing on generating brand-specific effectiveness data in Europe.

As with all vaccines, Vaxigrip® Tetra may not fully protect all persons who are vaccinated.

2.4 Summary of safety concerns

No important risks were identified for Vaxigrip® Tetra during clinical trials.

Table 5: Important identified risks

Risk	What is known	Preventability
Not applicable	Not applicable	Not applicable

Vaxigrip® (the trivalent formulation) has been in use for more than 14 years and more than 1.3 billion doses of this vaccine have been distributed worldwide. During this post-authorization use, some adverse events were observed and are considered as important identified or potential risks for Vaxigrip®. Given the similarity between TIV and QIV, these adverse events can potentially occur with the Vaxigrip® Tetra, they are considered as important potential risks for this vaccine.

Table 6: Important potential risks

Risk	What is known
• Allergic reactions leading to medical emergency with a failure of the circulatory system to maintain adequate blood flow to the different organs (shock) in rare cases • Pain situated on the nerve route (neuralgia); fits/seizures (convulsions) associated with fever; and nervous system disorders that may results in neck stiffness, confusion, numbness, limb pain and weakness, loss of balance, loss of reflexes, or paralysis of all or part of the body (encephalomyelitis, neuritis, Guillain-Barré syndrome) • Blood vessel inflammation (vasculitis) that could cause a skin rash and in very rare cases, temporary renal problems	Observed following the more than 14-year use of Vaxigrip® corresponding to more than 1.3 billion doses distributed worldwide but were not seen in the clinical trials for Vaxigrip® Tetra involving 5745 subjects, considered as important potential risks
• Temporary reduction in the number of certain types of particles in the blood called platelets; a low number of these can result in excessive bruising or bleeding (transient thrombocytopenia	One case of transient thrombocytopenia related to Vaxigrip® Tetra was observed during clinical trials. Observed following the more than 14-year use of Vaxigrip® corresponding to more than 1.3 billion doses distributed worldwide, considered as important potential risks
• Off-label use:intentional or unintentionaluse in children below 3 years of age	Vaxigrip® Tetra is indicated for patients over 3 years of age. As the Applicant's current trivalent influenza vaccine is indicated for use in those over the age of 6 months, potential misuse of the quadrivalent influenza vaccine could be expected in patients between 6 months and < 3 years of age As the manufacturing processes of both vaccines are very similar, it is not anticipated that there will be more adverse events after vaccination with the quadrivalent vaccine

During the development of Vaxigrip® Tetra, some populations were not studied, and therefore are considered as missing information at this stage of development.

Table 7: Missing information

Risk	What is known
Children below 3 years of age	As the manufacturing processes of Vaxigrip® Tetra and Vaxigrip® are very similar, it is not anticipated that vaccination with Vaxigrip® Tetra will result in more adverse events than after Vaxigrip® in case of use in children below 3 years of age
Pregnant or lactating women	Experience gathered from worldwide inactivated trivalent influenza vaccine use indicate that the vaccine is safe in pregnant or lactating women Results from animal studies with Vaxigrip® Tetra did not indicate direct or indirect harmful effects
Patients with lowered immunity either due to their medical history or to concomitant medication	Information on the use of inactivated trivalent influenza vaccines in patients with lowered immunity is limited A clinical study with Vaxigrip® in recipients with renal transplant and receiving medication lowering their immunity showed that vaccination (inactivated influenza vaccine) was safe and well tolerated. Other studies with inactivated trivalent influenza vaccines from other manufacturers showed that the vaccine was safe in patients with lowered immunity such as HIV positive patients. As with other vaccines is anticipated that patients with lowered immunity could have a reduced response to Vaxigrip® Tetra.
Vaccine efficacy/effectiveness	As with all vaccines, Vaxigrip® Tetra may not fully protect all persons who are vaccinated. Data on the protective effect of the vaccine will be obtained from a clinical study in children from 6 to 35 months (GQM05) Once the vaccine is marketed, The Global Influenza Hospital Surveillance Network may provide information on the influenza vaccine effectiveness in several countries worldwide (Spain, China, Turkey, Brazil, the Czech Republic and the Russian Federation) pending sufficient vaccine coverage In addition, the Joint vaccine European manufacturers initiative is under preparation

3 Summary of additional risk minimization measures by safety concern

Since the manufacturing process of Vaxigrip® Tetra was developed on the basis of the one used for Vaxigrip®, the more than 14-years of data from more than 1.3 billion doses distributed worldwide with Vaxigrip® are considered as supportive data when anticipating the safety profile of Vaxigrip® Tetra.

Based on the data available for both Vaxigrip® Tetra and Vaxigrip®, routine pharmacovigilance activities and routine risk minimization activities are considered sufficient, no additional risk minimization measure is deemed necessary for Vaxigrip® Tetra".

4 Planned post authorization development plan

4.1 List of studies in post-authorization development plan

Table 8: List of studies in post authorization development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of final results
GQM05: Efficacy and Immunogenicity Study of Quadrivalent Influenza Vaccine Administered via the Intramuscular Route in Healthy Children Aged 6 to 35 Months (randomized, double-blind placebo-controlled trial)	Evaluate efficacy against placebo, immunogenicity and safety profile	Missing efficacy information in children	Ongoing	Not yet known
Supportive program: Global Influenza Surveillance Network (GIHSN)- hospital-based, prospective, multi-country and multi-season, case-control study (non-Sanofi Pasteur specific data)*	Document strain circulation by season, burden of severe influenza (leading to hospitalization) and provide information on vaccine effectiveness against hospitalizations associated with influenza infection pending sufficient vaccine coverage rate in the EU countries	Need for continuous evidence on effectiveness of influenza vaccine	Ongoing for licensed influenza vaccines	Yearly in Periodic Safety Reports publication of results

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of final results
Supportive program: JIVES: Joint European manufacturers approach together with EMA and ECDC is under discussion	Operational research project focusing on brand vaccine effectiveness data collection	Feasibility of brand specific IVE, public-private joint analysis of results, communication of results to lay audience	Under preparation for 4 years (Jan 2016- Jan 2020).	Yearly in periodic safety reports

*This program was not implemented specifically for Vaxigrip® Tetra but for licensed influenza vaccines in general; it is considered as supportive.

4.2 Studies which are a condition of the marketing authorization

Not applicable.

5 Summary of changes to the Risk Management Plan over time

Table 9: Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
3.0	31 July 2015	Identified risks: None	Not applicable
		Potential risks: Adverse events of special interest: • Anaphylactic reaction • Convulsions (including febrile) • Guillain-Barré Syndrome • Encephalitis/myelitis • Neuritis (including Bell's palsy • Vasculitis • Thrombocytopenia Off-label use in children below 3 years of age	
		Very rare unanticipated AEs that could not be identified during the clinical development At the time of this RMP version, QIV has not been studied in: • Children below 3 years of age • Pregnant or lactating women • Immuno-compromised patients Vaccine efficacy/effectiveness	
2.0	25 October 2013	Identified risks: None	Not applicable
		Potential risks: Adverse events of special interest: • Thrombocytopenia • Anaphylaxis • Guillain-Barré Syndrome • Convulsions (including febrile) • Neuritis (including Bell's palsy) • Encephalitis / myelitis • Vasculitis Off-label use in children below 9 years of age	

Version	Date	Safety Concerns	Comment
		Missing information: Very rare unanticipated AEs that could not be identified during the clinical development At the time of this RMP version, QIV has not been studied in: • Children below 9 years of age • Pregnant or lactating women • Immuno-compromised patients • Patients with co-morbidities, sub-populations with genetic polymorphisms or patients of different ethnic origins Vaccine efficacy/effectiveness	
1.0	31 January 2012 (Previous marketing authorization application withdrawn by the Applicant)	Identified risks: None	Not applicable
		Potential risks: Adverse events of special interest: • Thrombocytopenia • Anaphylaxis • Guillain-Barré Syndrome • Convulsions (including febrile) • Neuritis (including Bell's palsy) • Encephalitis / myelitis • Vasculitis	
		Missing information: Very rare unanticipated AEs that could not be identified during the clinical development At the time of this RMP version, QIV has not been studied in: • Pregnant or lactating women • Immuno-compromised patients • Patients with co-morbidities, sub-populations with genetic polymorphisms or patients of different ethnic origins Vaccine efficacy/effectiveness	