RISK MANAGEMENT PLAN

Active substance(s) (INN or common name):	Haemagglutinin of three strains of influenza virus, two A strains and one B strain. The strains selected each year depend on the annual WHO recommendation
Pharmaco-therapeutic group (ATC Code):	Influenza Vaccines J07 CA 02
Name of Marketing Authorisation Holder or Applicant:	GlaxoSmithKline Biologicals S.A.
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	Fluarix™, Influsplit SSW™, α-RIX™

Data lock point for this RMP : 30 April 2015

Version number: 3.1

Date of final sign off: 21 May 2015

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Influenza (the flu) is one of the most common infectious diseases. It is caused by a virus (a germ). Three types of influenza viruses are known to cause illness in people. Most people get sick from influenza type A or B. The parts of the virus which make you sick are called antigens. Antigens can change from year to year, producing different "strains" of influenza A and B. This is why, even if you have already become ill with one strain of influenza A virus, for example, you can still get sick from the influenza B virus, or a different strain of influenza A virus. The risk of getting sick with flu depends on many things, including the climate you live in, whether there is an outbreak in your community, your age, whether your body has the ability to fight the strain of virus, and your general health.

As viruses that cause the regular flu usually change a little bit each year, a new flu vaccination (flu shot) is recommended every year. Each year, the World Health Organization (WHO) decides which strains are most likely to infect people and this determines which strains of flu A and flu B will be included in the seasonal flu shots.

Flu most often causes upper respiratory tract infections, including runny nose, cough, headache, nausea, and aches and pains. However, flu can affect the nervous system, and increase your chance of developing serious illnesses, such as pneumonia (lung infection). Flu can be severe enough to cause death.

In the US, approximately 30 to 60 million people get the flu every year. The flu results in about 200,000 hospitalizations a year [Sullivan, 1993; Thompson, 2003; Thompson, 2004]. A recent study in the US showed that the average number of deaths caused by the flu was 23,607 for the each year between 1976 and 2007 [CDC, 2010]. Flu-related complications (such as ear infections, sinus infections), hospitalizations and deaths are higher in children less than 5 years of age, persons with underlying medical conditions and adults 65 years of age and above [CDC, 2008b]. The frequency of flu diagnosed by doctors using lab tests in people older than 65 years can rise up to 47 cases per 1000 person-years [Nicholson, 1999]. At least one study also has shown a rise in death rates for lung infections and heart disease during the flu season. A recent study in the US from 1968 to 2001 showed that in average, 32 000 of the 600 000 deaths a year among the adults over the age of 65 years are due to flu [Simonsen, 2005].

Flu is an important cause of sudden onset of illnesses involving the lungs and breathing passages in children. Several studies have shown that flu causes hospitalizations and doctor's visits among children of all ages [Izurieta, 2000; Neuzil, 2000, O'Brien 2004]. A recent study showed that up to 10% of all children less than 14 years of age visited their health care provider with the flu in Italy [Paget, 2010]. Every year, 20-30% of children become infected with flu [Neuzil, 2002a]. During regular flu season, more than 40% of preschool-children and 30% of school-age children get the flu [Neuzil, 2000].

One recent study in the US has shown that for every 1000 children under 5 years of age, there were 6 to 27 emergency room visits and 95 clinic visits during the flu

season [Poehling, 2006]. In general, children with underlying medical conditions have an increased chance of complications from the flu than healthy children [Neuzil, 2000].

Complications associated with influenza infection include ear infections, sinus infections, severe pneumonia, additional bacterial infections, inflammation of the heart muscle, muscles and brain [Heikkinen, 2006]. In terms of death, the Center for Disease Control and Prevention (CDC) estimates that each year, 92 flu-related deaths occur in children less than 5 years of age in the United States [Thompson, 2003]. Of the 153 influenza-related deaths among children less than 18 years of age during the 2003/2004 influenza season in the US, 63% occurred in those less than 5 years old [Bhat, 2005].

The costs associated with the flu in the US are estimated at over $10 billion per year [HSC, 2005]; this includes not only the cost of hospitalizations, but also the cost of medicines, doctors' office visits, days lost from work, and getting less work completed due to not feeling well. Children are especially likely to get sick from the flu virus, and often spread the virus into the communities and households where they live and play [Longini, 1982; Fox, 1982].

Additional important effects of flu infection in children include the use of antibiotics unnecessarily, lost work time for caregivers and additional illnesses among family members. In the US, flu accounts for 10-30% of excessive antibiotic use during the winter in children less than 15 years of age [Neuzil, 2000], resulting in an average of 20 days of parental time off work and 22 episodes of additional illness among family members per 100 children followed up [Neuzil, 2002].

VI.2.2 Summary of treatment benefits

Flu shots are the principal means of preventing flu and associated complications. Flu shots need to be given every year for protection against the flu because flu viruses can change every year. Therefore, each year, a new flu shot is made.The seasonal flu shots contain 3 flu virus strains that are designed to protect a person against 3 types of flu viruses at the same time. That's why they are called Trivalent (meaning three) Influenza Vaccines (TIV). In adults, a recent published paper showed 59% efficacy (the ability to produce a protective effect) of TIV in adults aged 18 – 65 years [Osterholm, 2012] against flu cases confirmed by lab tests. Efficacy in persons > 65 years of age is supported by reduced number of death for any reason (47%) and in hospital admissions for flu or pneumonia (27%), illness of the breathing passages (22%), or heart disease (24%) [Jefferson, 2005].

The seasonal flu shots are 67% effective in healthy children against the flu cases confirmed by doctors using lab tests, and 51% effective against acute middle ear infection [Manzoli, 2007]. Recent estimates from the US show that starting a vaccination program for children 6 to 59 months of age could prevent about 2,250 hospitalizations and 650,000 outpatient visits per year, [Lewis, 2007]. In addition, a study of how much having the flu may cost has shown that giving flu shots regularly to children 6 months to 18 years old is cost saving [Weycker, 2005]. Studies have also indicated that giving flu shots to children is likely to be effective in stopping the spread of flu within families and communities [Monto, 1970; Reichert, 2001]. Giving flu shots to 85% of school-age children in one community in the US reduced

the incidence of illnesses involving the breathing passages by three-fold (3 times) when compared to a community where school-age children did not receive flu shot [Monto, 1970]. Information from Japan has also shown that giving flu shots to 50% to 85% of school-age children reduced the number of deaths across all age groups, with the most number of deaths reduced seen in the adults 65 years of age and older [Reichert, 2001]. It has been estimated that giving flu shots to 20% of school-age children could reduce overall number of deaths in the older adults (above 65 years of age) by a greater amount than giving flu shots to 90% of the older adults directly [Halloran, 2006]. Furthermore, giving flu shots to 50% to 70% of children could control the flu during the flu season every year [Longini, 2000; Halloran, 2002]. Thus, giving flu shots to children has the potential to reduce the occurrence of flu illness in the community.

In clinical studies, the ability of the FLU D-TIV vaccine to help protect against flu was demonstrated in both children and adults.

VI.2.3 Unknowns relating to treatment benefits

Not Applicable.

VI.2.4 Summary of safety concerns

Important identified risks

There have been no important identified risks identified with the usage of Flu D-TIV during the clinical development program.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Life-threatening allergic reaction (anaphylaxis)	Life-threatening allergic reactions have been reported in people who had flu shot. People allergic to any ingredients in Flu D-TIV vaccine could have an allergic reaction to flu shot. The viruses for the flu shot are grown in eggs; therefore, people allergic to eggs could have an allergic reaction to Flu D-TIV. The majority of reactions probably are caused by residual egg protein in the vaccine [CDC, 2010b].
Fits when having fever (febrile convulsion)	In April 2010, there was a reported increase in febrile convulsion following influenza vaccination in young children in Western Australia. Following extensive investigations into this safety issue, epidemiological analyses determined that administration of the 2010 seasonal influenza vaccines, Fluvax® and Fluvax Junior® (manufactured by Bio CSL), was associated with an increased risk of febrile convulsions. The rate of febrile convulsions was found to be up to 1 per 100 (1%) children under age 5 years vaccinated with this vaccine [TGA, 2010], but the risk has not been confirmed for other influenza vaccines, including Flu-D-TIV.
Inability to move one side of the face (Bell's palsy)	Bell's palsy has been reported in people who had flu vaccine within the nose. Researchers have not found a link between Bell's palsy and flu vaccines that are given by injection.
Paralysis that starts in the feet and moves up (Guillain-Barré syndrome or GBS)	GBS has been reported to occur in approximately 1 or 2 people out of every million people who receive seasonal flu shot.
Injection site bleeding in patients	Bleeding may occur at the injection site in populations at increased risk of

Risk	What is known (Including reason why it is considered a potential risk)
with blood clotting illness (Injection site hemorrhage in individuals with thrombocytopenia or any coagulation disorder)	hemorrhage, such as those with thrombocytopenia or acquired/hereditary coagulation disorders.
Administration error due to mix-up of vaccine brands	Administration errors due to mix-up of two vaccine brands may occur when two vaccines with similar brand names are co-marketed in the same country.
Excessive daytime sleepiness and sudden attacks of sleep (Narcolepsy)	Early laboratory results suggest a homologous sequence between hypocretin, the protein that controls the sleep-wake cycle, and a protein on the surface of the H1N1 flu virus, in samples from unvaccinated narcoleptic patients. However, to date, there is no clinical evidence suggesting that the H1N1 viral protein used in seasonal flu shot increases the risk of narcolepsy. Even though further research is needed to understand whether exposure to H1N1 viral protein in wild virus or seasonal flu shots may be linked with an increased risk of narcolepsy, GSK has decided to include narcolepsy as a potential risk in Risk Management Plans for GSK H1N1-containing seasonal influenza vaccines, including Flu D-TIV, as a precautionary measure.

Missing information

Risk	What is known
Use during pregnancy and lactation	The safety of Flu D-TIV when administered to pregnant or breast-feeding women has not been evaluated.

VI.2.5 Summary of additional risk minimisation measures by safety concern

Not Applicable.

VI.2.6 Planned post authorisation development plan

List of studies in post authorisation development plan

Not applicable

Studies which are a condition of the marketing authorisation

Not Applicable.

VI.2.7 Summary of changes to the Risk Management Plan over time

There has been no Risk Management Plan (RMP) submitted in the EU given that Flu D-TIV has been licensed for over 20 years and has a well established safety profile.

However, GSK Biologicals submitted a Risk Management Plan (Version 1, dated 07 December 2011) based on the EU RMP template at the request of the Therapeutic Goods Administration (TGA), as a condition of registration for all seasonal influenza vaccines with a paediatric indication that were not supplied in Australia in 2010.

Since version 1, the RMP has been updated in June 2014 (version 2), which is summarized below:

- The RMP has been updated to the new EU RMP template format.
- The potential risks were updated to align with the Flu D-QIV RMP. The potential risks for Flu D-TIV are: Anaphylaxis, Febrile seizure, Bell's palsy, Guillain-Barré Syndrome, Injection site haemorrhage in individuals with thrombocytopenia or any other coagulation disorder, Administration error due to mix-up of vaccine brands, and Narcolepsy.
- Furthermore, in response to the Interim Guidance on Enhanced Safety Surveillance for Seasonal Influenza Vaccines in the EU (EMA/PRAC/135943/2014), a statement was added on GSK's proposal for the enhanced safety surveillance.
- The EMA issued the Interim Guidance on Enhanced Safety Surveillance for Seasonal Influenza Vaccines in the EU (EMA/PRAC/135943/2014) on 10 April, 2014.
- GSK's plan to meet the requirements specified in the guidance. In May 2015, the company updated the Flu D-TIV RMP to version 3, with information that was requested by PEI regarding the Epi – 045 study.