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Public Assessment Report

Scientific discussion

Vaxigrip Tetra
Quadrivalent Influenza Vaccine
(split virion, inactivated)

DE/H/1949/001/DC

Date: January 2019

This module reflects the scientific discussion for the approval of Vaxigrip Tetra. The procedure was finalised at 21. June 2016. For information on changes after this date, please refer to the module 'Update' in Chapter VII. Updates since the PAR from November 2016 are highlighted in yellow. Minor editorial corrections are not highlighted.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for *Vaxigrip Tetra* (CZ, DE, ES, HU, IT, SK), *VaxigripTetra suspension injectable en seringue préremplie* (BE), *VaxigripTetra* (BG, EE, EL, FI, FR, IS, HR, LV, LU, MT, NL, PL, PT, RO, SE, SI, CY), *Vaxigriptetra* (DK, NO), *Quadrivalent influenza vaccine (split virion, inactivated)* (IE, UK), *VaxigripTetra injekcinė suspensija užpildytame švirkšte* (LT), *VaxigripTetra Injektionssuspension in einer Fertigspritze* (AT), from Sanofi Pasteur. The marketing authorisation application (MAA) was submitted on 01.10.2015 as a decentralised procedure and positively closed on 21.06.2016.

The product is indicated for active immunisation of adults and children from 6 months of age for the preventions of influenza disease caused by the two influenza A virus subtypes and the two influenza B virus types contained in the vaccine.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 28 of Directive 2001/83/EC as amended.

II. QUALITY ASPECTS

II.1 Introduction

Vaxigrip Tetra is a quadrivalent influenza-virus vaccine, presented as suspension for injection in prefilled syringe, containing the split surface antigens of influenza viruses from two A strains (H1N1 and H3N2) and two B strains (B Victoria and B Yamagata lineage) Its Anatomical Therapeutic Classification (ATC) is J07BB02.

Vaxigrip Tetra contains purified haemagglutinin (HA) and neuraminidase (NA) antigens from the split surface of each of the four influenza virus strains, types A and B, as recommended annually for immunisation by the World Health Organisation (WHO), Center for Biologics Evaluation and Research (CBER) and the European Union for the Northern Hemisphere in the formulation.

The influenza virus strains are individually grown in embryonated chicken eggs. The allantoic fluid is harvested, clarified by centrifugation and filtration, and then concentrated by ultrafiltration. The viral particles are purified by isopycnic ultracentrifugation in a sucrose gradient, split by octoxynol-9 and inactivated by formaldehyde, which results in 4 monovalent bulks for each strain. The drug product is obtained by formulation of the 4 drug substances in a Phosphate buffered Saline without preservatives into a sterile suspension.

The potency of the vaccine is expressed as the amount of the HA protein per dose.

Each 0.5 ml of the vaccine has the following composition:

Active Ingredient:

Purified antigen fractions of

- Monovalent inactivated split-virion: A/H1N1 15 µg
- Monovalent inactivated split-virion: A/H3N2 15 µg
- Monovalent inactivated split-virion: B strain (Victoria lineage) 15 µg
- Monovalent inactivated split-virion: B strain (Yamagata lineage) 15 µg

Other ingredients:

- Sodium chloride
- Potassium chloride
- Disodium phosphate dihydrate
- Potassium dihydrogen phosphate
- Water For Injections

II.2 Drug Substance

The drug substance is composed of inactivated split-virus antigen of each of the four strains recommended by the WHO for inclusion in the quadrivalent influenza vaccine. Two of these strains are from A subtypes and two of B types. The second B strain belongs to the opposite lineage (Yamagata/Victoria) as the strain currently recommended for trivalent composition.

- *Manufacture*

A master and a working seed were prepared for each of the virus strains, received from the WHO collaborating centres. The manufacturing process for the monovalent bulk is similar to the well-known manufacturing process for the monovalent bulks of the company's trivalent vaccine Vaxigrip. The only change implemented at the drug substance level is at the final dilution step. The change became necessary in order to increase the concentration of the antigen in the monovalent bulk, to allow formulation of the final vaccine. The manufacturing process can be divided into four main parts:

- Propagation of the working seed in fertilized hen's eggs, harvesting of infected allantoic fluid followed by clarification, filtration and concentration.
- Purification of the virus particles by ultracentrifugation using a sucrose gradient
- Splitting of the virus particles with octocxnol-9
- Inactivation of the viral suspension using formaldehyde, followed by sterile filtration

- *Control of Materials*

The following starting materials used in the production of the drug substance are of biological origin: influenza seed virus, eggs.

The testing of the virus and the eggs is the same as for Vaxigrip. Sufficient detailed information has been provided on the control and source of the starting materials.

- *Process validation*

Critical steps of the drug substance production process have been identified and are sufficiently controlled. Process consistency has been demonstrated on at least three consecutively produced commercial scale batches for each subtype.
Inactivation studies performed on different strains have demonstrated complete inactivation of all four influenza strains.

- *Characterisation and specification*

Characterisation focused on the analysis of the identity, integrity of the antigen, the protein profile and particle size, the immunological properties of the virus surface antigens and on the purity of the drug substance antigens. Product and process related impurities are either controlled by routine release testing or it was shown that they could be eliminated to acceptable levels through validation studies. The specifications are essentially the same as the one for the trivalent vaccine Vaxigrip. The active pharmaceutical ingredients in influenza split vaccines are viral haemagglutinin and neuraminidase proteins. Appropriate identity tests of these proteins and an enzymatic activity test for Neuramindase were conducted. All analytical methods have been appropriately validated.
The monovalent bulks are filled and stored in 45 L stainless steel or 50 L polypropylene container.

Stability
A shelf life of 24 months at +5°C ± 3°C has been granted for all subtypes.

II.3 Medicinal Product

Vaxigrip Tetra is a quadrivalent inactivated, split virion seasonal influenza vaccine. It contains four influenza strains, two A (A/H1N1 and A/H3N2) and two B (one each of the Yamagata and Victoria lineages) strains. The selection of strains follows recommendations by the World Health Organization which started with the season SH (southern hemisphere) 2013 with official recommendations for a fourth influenza strain.

- *Pharmaceutical development*

Vaxigrip Tetra drug product development is based on Sanofi Pasteur`s licensed seasonal trivalent influenza vaccine Vaxigrip, taking into consideration the addition of a fourth active substance. It is formulated to a minimum HA concentration of 15 µg HA per strain per 0.5 mL dose. The same excipients are found in both vaccines. There is no excipient of human or animal origin, or novel excipient in the vaccine.

- *Manufacture of the product*

The manufacturing process for the Vaxigrip Tetra drug product has been developed based on the Vaxigrip drug product manufacturing process and consists of the following steps:

- Formulation of the final bulk;
- Transfer of the final bulk into SP network for filling (when filling takes place outside the formulation site);
- Filling (including stoppering) and inspections of the final containers;
- Transfer of the final containers into SP network for labeling and packaging (when labeling and packaging take place outside the filling site);
- Labeling and packaging of the Vaxigrip Tetra final product.

The process uses the same starting materials, equipment and facilities as Vaxigrip. The development of the manufacturing process is limited to the production scale-up and to technical adjustments during the formulation process.

- *Product specifications*

Compliance with the product specifications has been shown on 3 final container lots of commercial scale. In addition to the "classical" SRD method a "bivalent" SRD method has been developed for the two influenza B strains in the quadrivalent formulation. The bivalent SRD assay should eliminate problems with cross-reactivity of the B Yamagata and B Victoria antisera.

Specifications for excipients and analytical procedures are in line with the Ph. Eur. Controls of final bulk product (bacterial and fungal sterility, appearance, pH value , extractable volume, HA Antigen content and identification by SRD, bacterial endotoxins). Methods are either in line with Ph. Eur. or have been adequately described and validated. The proposed shelf-life of 12 months for the Vaxigrip Tetra final product by storage at 2 to 8°C could be granted.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Collectively, quality data are considered adequate to support the initial marketing authorisation.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The quadrivalent influenza vaccine (QIV) has been developed based on the knowledge in terms of manufacturing process and controls of Vaxigrip, a licensed trivalent influenza vaccine manufactured by Sanofi Pasteur. Nonclinical evaluation for Vaxigrip Tetra included immunogenicity in a mouse study, systemic and local toxicity in a repeat-dose toxicity study and a developmental and reproductive toxicity study. QIV lots used in nonclinical safety studies are clinical batches that were manufactured with industrial manufacturing process and following GLP principles. Conduct of these studies was claimed in accordance with the EMA and WHO relevant Guidelines.

In addition, for registration purpose in some international countries and despite the absence of specific concerns, a non-GLP compliant safety pharmacology study was conducted.

III.2 Pharmacology

A primary pharmacodynamic study was performed in mice and demonstrated a clear dose response within a range from 1/27 human dose to full human dose administered subcutaneously. After a single vaccination, sustained Haemagglutination Inhibition (HI) responses against two A strains were detected with mean HI titers ranging from 14 to 376 for the A/California/7/2009 (H1N1) and from 13 to 243 for the A/Texas/50/2012 (H3N2) strain. After the second immunization, HI titers to two A strains were further increased and meanwhile HI responses against two B strains were also detected with positive antigen dose effect evidenced. These data provide a rationale for including the additional B strain in vaccine.

A supportive safety pharmacology study was performed with QIV candidate in rabbits. A single and repeated (3 injections 2 weeks apart) intramuscular administration of a filled product of QIV did not cause overt adverse effect on cardiovascular and respiratory functions, and body temperature. Data are supported by those of a pivotal repeat-dose toxicity study and consistent with clinical trial data suggestive of no overt adverse effect of QIV candidate on the vital functions.

III.3 Pharmacokinetics

No dedicated pharmacokinetic studies were performed, which is acceptable, according to the relevant regulatory Guidelines.

III.4 Toxicology

A pivotal GLP-compliant local tolerance and repeat-dose toxicity study was performed in rabbits using the human dose under intramuscular route. Following up to three intramuscular injections at two-week intervals, no adverse systemic effects were observed. The observed QIV-related effects were limited to minimal and transient macroscopic and microscopic findings consistent with local reaction at the injection site. At the end of the recovery period, data showed a partial recovery of the local inflammation seen at the injected muscle.

In a pivotal GLP-compliant developmental and reproductive toxicity study, groups of rabbits were dosed five times intramuscularly with one human dose of QIV prior to mating (2 doses) and during gestation (3 doses) to evaluate the effects on the embryo-fetal and early post-natal developments. There was no indication of maternal systemic toxicity induced during the gestation and lactation periods with no unscheduled deaths and no adverse clinical signs. There was no effect on the mating performance and female fertility. There was no indication of a teratogenic potential and no effect on pre and post-natal development. Antibodies to the vaccine were demonstrated both in the dams and in the foetuses.
Currently, no data on male fertility is available, which can be acceptable, according to the EMA Guidelines.

III.5 Ecotoxicity/environmental risk assessment (ERA)

No risk to the environment is expected from the use of the QIV candidate.

III.6 Discussion on the non-clinical aspects

Nonclinical pharmacology data for QIV provided a rationale for including the second B strain in the vaccine formulation. Nonclinical safety testing of QIV did not raise any safety concerns and under the testing conditions, the vaccine was well-tolerated and was not teratogenic. The results are in accordance with those observed in clinical trials. Collectively, nonclinical evaluation of QIV is considered adequate for support of initial MAA.

IV. CLINICAL ASPECTS

IV.1 Introduction

Annual vaccination is the most effective method for the prevention of influenza disease and is currently mainly performed with trivalent influenza vaccines (TIV) containing two A strains (H1N1 and H3N2) and one B strain. The efficacy of the trivalent vaccines is dependent on how closely the strains included in the vaccines match the circulating virus. Recommendations relative to vaccine composition are issued annually by the WHO, CBER and the European Union. From the late 1970's, influenza B viruses have diverged into two genetically distinct phylogenetic lineages on the basis of their haemagglutinin. Since the mid 1980's the two lineages, represented by the influenza B/Victoria/2/87 and B/Yamagata/16/88 strains, have been co-circulating in varying proportions in different years and countries. Since only one single influenza B strain is included in the currently licensed trivalent seasonal influenza vaccines, each season there is a risk of mismatch between the B strain recommended for inclusion in the trivalent influenza vaccines and the dominant circulating B strain, which may vary geographically. To address the issue of potential sub-optimal protection of the TIV against circulating B lineages, Sanofi Pasteur has developed a split virion, inactivated, quadrivalent influenza vaccine (QIV), that contains, in addition to the three strains annually recommended by WHO and included in Sanofi Pasteur`s commercial Vaxigrip trivalent vaccine (two A-strains, currently A/H1N1 and A/H3N2, and one B-strain), a second B strain, belonging to the opposite lineage as the B strain currently recommended for trivalent vaccine (TIV) composition, and that is shown to co-circulate in the human population. The QIV will be indicated for active immunization of adults and children from 6 months of age and older for the prevention of influenza disease caused by the 2 influenza-A virus subtypes and the 2 influenza-B virus types contained in the vaccine.

IV.2 Pharmacokinetics

Pharmacokinetic studies were not performed, as they are not considered applicable. This is in accordance with the note for guidance on clinical evaluation of vaccines (CPMP/EWP/463/97).

IV.3 Pharmacodynamics

The mechanism of action of the influenza vaccine consists of the induction of immune responses against the viral antigen components contained in the formulation. Thus, the pharmacodynamic profile of the QIV is defined by its immunogenicity profile.

IV.4 Clinical efficacy

Five Phase III studies (GQM11, GQM02, GQM09, GQM01 and GQM04) were conducted to evaluate the immunogenicity of the candidate vaccine QIV in 18 to 60-year-old adults, the elderly > 60 years, and in paediatric subjects from 3 to 17 years of age. Vaccine efficacy was also evaluated in children aged 6 to 35 months in study GQM05. The studies were summarized in Table 1.

The 6 clinical studies supported the application for the use of the QIV in children > 6 months and adults.

Table 1 Summary of Phase III clinical studies supporting the QIV development

Study/ Status	Main Objectives of the Study Presented in the Application	Study Design	Test Products	Study Population
GQM11 completed	- Equivalence of the immune response of 3 lots of QIV - Non-inferiority of the immune responses induced by QIV compared with the TIV - Superiority of the immune response to each B strain in the QIV compared with the TIV that does not contain the corresponding B strain - Descriptive immunogenicity assessed by the HAI and SN assay - Descriptive safety of QIV compared with the TIV	Phase III, randomized, double-blind for subjects in the QIV and TIV2 groups, single-blind up to D21 for subjects in the TIV1 group*, active-controlled, multi-center study in Poland, France, Germany, and Belgium	QIV manufactured with the drug substance final process, or TIV1 containing the B strain from the Victoria lineage or TIV2 containing the B strain from the Yamagata lineage (the licensed TIV for the 2014-2015 season)	1111 adults aged 18 to 60 years enrolled: QIV: 833, TIV1: 140, TIV2: 138 1108 elderly aged > 60 years enrolled: QIV: 833, TIV1: 138, TIV2: 137
GQM02 Completed;	- Non-inferiority of the immune responses induced by QIV compared with the TIV - Superiority of the immune response to each B strain in QIV compared with the TIV that does not contain the corresponding B strain - Descriptive immunogenicity assessed by the HAI assay, the SN assay, and ELLA - Descriptive safety of the QIV compared with the TIV	Phase III, randomized, double-blind, active-controlled, multi-center study in Poland, Finland, Mexico, and Taiwan	One or 2 injections of QIV manufactured with the drug substance final process or TIV1 containing the B strain from the Victoria lineage or TIV2 containing the B strain from the Yamagata lineage (the licensed TIV for the 2013-2014 season).	Children aged 3 to 8 years enrolled: 1242 QIV: 887, TIV1: 181, TIV2:174
GQM09 Completed;	- Descriptive immunogenicity of the QIV - Descriptive safety of the QIV	Phase III, open-label, no control arm, multi-center study in Taiwan	One injection of QIV manufactured with the drug substance final process	Children / adolescents aged 9 to 17 years enrolled: QIV: 100
GQM01 Completed;	- Non-inferiority of the immune responses induced by QIV compared with the TIV - Superiority of the immune response to each B strain in the QIV compared with the TIV that does not contain the corresponding B strain - Descriptive immunogenicity assessed by the HAI and SN assays - Descriptive safety compared with the TIV	Phase III, randomized, active-controlled, multi-center trial, double-blind for QIV and TIV1, open-label for TIV2 in France and Germany*	One injection of QIV manufactured with the drug substance initial process or TIV1 containing the B strain from the Victoria lineage (the licensed TIV for the 2011-2012 season) or TIV2 containing the B strain from the Yamagata lineage	783 adults aged 18 to 60 years enrolled: QIV: 559, TIV1: 113, TIV2: 111 785 elderly subjects aged over 60 years enrolled: QIV: 558, TIV1: 113, TIV2: 114
GQM04 Completed;	- Equivalence of the immune response of 3 lots of QIV - Descriptive immunogenicity assessed by the HAI and SN assays - Descriptive safety compared with the TIV	Phase III, randomized, double-blind (for QIV lots), open-label (for QIV or TIV receipt), active-controlled study in Australia and the Philippines	One injection of either 1 of 3 lots of QIV manufactured with the drug substance initial process, or TIV (the licensed TIV for the 2011-2012 season)	385 children / adolescents aged 9 to 17 years enrolled: QIV: 330, TIV: 55 1705 adults aged 18 to 60 years enrolled: QIV: 1659, TIV: 56
GQM05 Completed	-Demonstration of clinical efficacy of 2 doses of QIV for the prevention of laboratory confirmed influenza illness in naïve subjects -Non-inferiority of antibody responses induced by QIV compared with the TIV -Demonstration of superiority of HAI antibody response to each B strain compared with the TIV that does not contain the corresponding B-strain -Descriptive immune response of a booster dose one year after QIV vaccination	Phase III, randomized, observer-blind, controlled, multi-center trial conducted in Spain, France, Greece, Italy, Romania, Dominican Republic, Honduras, South Africa, and The Philippines	Two injections of either, QIV, Placebo, TIV1, or TIV 2 One year later booster dose QIV or Placebo QIV: 209 Placebo: 40	5.806 children aged 6 to 35 months, not previously vaccinated against influenza enrolled: QIV: 2.721 Placebo: 2.715 TIV1: 183 TIV2: 186

Study/ Status	Main Objectives of the Study Presented in the Application	Study Design	Test Products	Study Population
	- Descriptive immunogenicity assessed by the HAI assay			

CSR: clinical study report, HAI: hemagglutination inhibition, SN: seroneutralization, ELLA: enzyme-linked lectin assay
*Studies GQM11 and GQM01 were double-blind for subjects in the QIV and the TIV groups containing the B lineage used in the licensed seasonal TIV, while the design was single-blind or open-label in the group receiving the B strain of the opposite lineage, to enable these subjects to receive the licensed seasonal influenza vaccine after the studies.

Of the 6 Phase III clinical studies that supported the application for the QIV, studies GQM11, GQM02, GQM09 and GQM05 were considered as the main/pivotal studies for characterization of the immunogenicity of the candidate vaccine QIV. The efficacy protection against influenza-infections of the QIV in populations aged 3 years and above is inferred from its immunogenicity based on comparative immunogenicity evaluation with Sanofi Pasteur's trivalent inactivated seasonal influenza vaccine (TIV) which is licensed in the European Union since 1998.
GQM11 (enrolled adults and elderly) and GQM02 (enrolled children aged 3 to 8 years) included two comparator groups, one receiving the trivalent influenza vaccine containing the strains recommended for the ongoing season, and one a second trivalent vaccine that contained a strain of the B lineage not included in the seasonal vaccine. The third pivotal study GQM09 enrolled children aged 9 to 17 years to evaluate data regarding safety and immunogenicity in this age group.
The efficacy of QIV to prevent laboratory confirmed influenza-infection after two doses of QIV compared to Placebo was evaluated in children aged 6 to 35 months who had not previously been vaccinated against influenza to confirm the QIV clinical benefit in the fourth pivotal study (GQM05) This study was conducted after initial approval of Vaxigrip Tetra to get the approval of the age indication extension from 6 months of age.

Two supportive Phase III studies GQM01 and GQM04 evaluated the candidate vaccine in adults, elderly and children from 9 years of age. GQM04 included a control group that received the seasonally recommended trivalent influenza vaccine, whereas GQM01 included control groups with trivalent influenza vaccine containing B strains of either the recommended or the B lineage not included in the seasonal influenza vaccine. Both studies were conducted with QIV batches from an initial Drug substance manufacturing process with a slightly higher than expected HA content for B strains (mainly in B/Florida).

Target indication and posology:
Within the evaluated studies for approval of the candidate vaccine the following indication and posology were shown to be effective for active immunisation of adults and children from 6 months of age for the prevention of influenza disease.

Proposed Indication:
The vaccine Vaxigrip Tetra is a quadrivalent vaccine and is indicated for active immunisation of adults and children from 6 months of age and older for the prevention of influenza disease caused by the two influenza A virus subtypes and the two influenza B virus types contained in the vaccine.

Proposed Posology:
The vaccine should be administered as a single 0.5 ml injection. Children from 6 months of age to less than 9 years of age who have not previously been vaccinated against influenza should receive a second dose of 0.5 ml after an interval of at least 4 weeks.

Revaccination:
Repeated vaccination with QIV was investigated in the efficacy study GQM05. A sub-group of previously vaccinated children in study GQM05 were revaccinated in the following season. Of note, this study covers only subjects from 6-35 month of age. The impact of revaccination on vaccine effectiveness in individuals older than those included in the clinical trial will be investigated during the post-marketing monitoring of that concern. Programs are implemented to estimate yearly vaccine effectiveness. The data collected within these programs will also provide further information regarding repeated vaccination in all vaccinated age groups, depending on the extent of use.

IV.5 Clinical safety

The safety of Vaxigrip Tetra (QIV) was evaluated in 6 clinical phase III trials (GQM11, GQM02, GQM05, GQM09, GQM01 and GQM04). The trials GQM01 and GQM04 were conducted with QIV batches from an initial drug substance (DS) manufacturing process with a slightly higher than expected HA content for B strains (mainly in B/Florida). These studies are considered supportive. Four other studies (GQM02, GQM09, GQM11, and GQM05) were conducted with QIV batches from a final commercial DS manufacturing process for which the HA content is in accordance with European Pharmacopoeia requirements for all strains. These trials are considered pivotal. The clinical trials were conducted in adults aged 18 to 60 years, the elderly aged over 60 years, and children and adolescents aged 3 to 17 years as well as in children aged 6 to 35 months. Two studies (GQM04 and GQM11) were conducted with 3 different QIV lots. Two formulations of Sanofi Pasteur`s trivalent influenza vaccine (TIV) Vaxigrip were used as a comparator in all studies except the open-label study GQM09. One formulation contained the B-strain recommended for the ongoing season, and one contained a strain of the B lineage not included in the seasonal vaccine. The safety of the QIV was also evaluated in influenza-naïve children aged 6 to 35 months (GQM05) in comparison with placebo and the two formulations of Sanofi Pasteur's trivalent influenza vaccine (TIV).

The size of the safety database is in accordance with the "Guideline for the evaluation of new vaccines" (EMEA/CHMP/VWP/164653/2005). As requested in this guideline, uncommon adverse events which occur at a frequency between 1/100 and 1/1000 vaccinated persons would have been reliably determined in the QIV trials.
In the studies conducted during the clinical development, the QIV was administered as one intramuscular or subcutaneous injection to subjects aged 9 years and above. One or two doses of QIV were administered to children aged 3 to 8 years, depending on their history of seasonal influenza vaccination at enrolment. All children were vaccinated twice in the efficacy trial GQM05, because they did not receive an influenza-vaccination before. A subgroup of these children received a third QIV/Placebo vaccination one year later to prove the boosterability of Vaxigrip Tetra. This schedule reflects official recommendations and experience with Sanofi Pasteur`s TIV and other inactivated influenza vaccines.
A total of 8.466 subjects received 1 or 2 injections of Vaxigrip Tetra (i.e., 3.040 adults 18 to 60 years of age, 1.392 elderly more than 60 years of age, 429 children and adolescents aged 9 to 17 years of age, 884 children aged 3 to 8 years, and 2.721 children aged 6 to 35 months, among them 2718 were followed for safety (SAEs including AESIs) and 1614 were followed for reactogenicity (solicited and unsolicited AEs) in addition to SAEs). The population for whom application is sought is in general adequately reflected in the clinical trials. Safety data are somewhat limited for the adolescent subgroup (429 children and adolescents 9 to 17 years of age). However, the clinical data generated in adults and younger children are considered appropriate to adequately evaluate the safety of the QIV also in this age subgroup.
The review of the available data has shown that Vaxigrip Tetra is safe and well tolerated with a safety profile comparable to that of the licensed TIV Vaxigrip and the comparator TIV 2 having the influenza B strain not contained in the licensed trivalent Vaxigrip in all age groups. In addition, the safety profile of the QIV is similar to that of the Placebo in children aged 6 to 35 months.

An integrated safety analysis of Studies GQM01, GQM11, GQM04, GQM09, and GQM02 was conducted to improve the precision of the safety profile of the QIV, as the assessment and analysis of safety data were similar across all these studies. The safety profile of the QIV is described based on the pooled data for subjects aged 9 years and above, and on individual study data for subjects aged 3 to 8 years, for whom safety data were available only from Study GQM02. For Studies GQM01, GQM02 and GQM11, the 2 TIV groups (containing either one of the two B-strain lineages) were pooled and presented as a single vaccine group as no major differences were observed in their safety profiles. For Studies GQM04 and GQM11, the 3 QIV lots were pooled and presented as a single vaccine group. The safety data in children aged 6 to 35 months were not included in the integrated analysis but are presented based on the individual study analysis.

Solicited adverse events

Solicited local and systemic reactions were collected from Day 0 to Day 7. Solicited reactions were always considered as related to vaccination. After the administration of both vaccines used in the clinical trials (i.e. the QIV and the two TIVs), a higher rate of solicited adverse reactions (ARs) was observed in children and adolescents compared with adults and elderly ones. This is the case for many vaccines. The majority of local and systemic ARs across all age and vaccine groups were graded as mild or moderate and resolved within 3 days or less.
The recorded solicited symptoms following Vaxigrip Tetra vaccination are consistent with those observed following vaccination with Vaxigrip in clinical trials. The occurrence of pain, the most frequently reported local AR in all age groups, was comparable between children 3 to 8 years of age (56.5% of subjects in the pooled QIV group versus 55.4% in the pooled TIV group), children and adolescents 9 to 17 years of age (54.5% of subjects each in the pooled QIV and the pooled TIV group) and adults 18 to 60 years of age (52.8% each, respectively). Lower incidences were seen in elderly (25.8% versus 22.3%, respectively). On the other hand, the occurrence of other local solicited ARs was markedly higher in children 3 to 8 years of age compared with children and adolescents 9 to 17 years of age. Erythema was reported by 20.4% of children 3 to 8 years of age in the pooled QIV and 22.3% in the pooled TIV group, compared with 9.8% of children and adolescents 9 to 17 years of age in the pooled QIV and 5.5% in the pooled TIV group. Swelling was reported by 20.5% and 20.1% versus 10.7% versus 7.3%, respectively and induration by 16.4% and 14.1% versus 6.8% and 7.3%, respectively. The occurrence of the aforementioned local reactions in adults and elderly were comparable to those observed in children and adolescents 9 to 17 years of age.
The most frequently reported solicited systemic ARs across all age groups from 3 years and above were headache, myalgia and malaise. Children from 6 to 35 months reported mostly appetite lost (28.9%), crying abnormal (27.1%), and fever (20.4%). Both, the TIV and the QIV were again more reactogenic in the younger age groups, mostly in children 3 to 8 years of age. Larger differences between the QIV vaccine group of children 3 to 8 years of age and children and adolescents 9 to 17 years were seen for fever (8.4% versus 2.3%), malaise (30.7% versus 20.3%), and shivering (11.2% versus 3.7%). The occurrence of myalgia (28.5% versus 29.1%) and headache (25.7% versus 24.7%) were comparable in the two age groups following vaccination with the QIV. No relevant differences were seen between children and adolescents 9 to 17 years of age and adults. Similarly as for local ARs, the occurrence of all solicited systemic ARs was notably lower in elderly. Imbalances between the QIV vaccine group and the TIV vaccine group in the integrated safety analysis were observed regarding systemic adverse reactions in the age cohort of children and adolescents 9 to 17 years of age. Myalgia was reported by 29.1% of subjects in the QIV versus 12.7% in the TIV vaccine group, fever by 2.3% versus 9.1% of subjects, respectively, and malaise by 20.3% versus 16.4% of subjects, respectively. It has to be noted, that these integrated safety analysis results were based on a small sample size in the TIV vaccine group unequal to the sample size in the QIV vaccine group (55 subjects in the pooled TIV group versus 429 subjects in the pooled QIV group). Additionally, the incidences of the adverse events of fever, myalgia, and malaise are within the same range in the two vaccine groups.

Unsolicited adverse events
The safety profile of the QIV is generally comparable to that of the TIV. In the QIV and the TIV vaccine groups, non-serious unsolicited adverse events were reported in a higher proportion of children 3 to 8 years of age compared with children and adolescents 9 to 17 years of age, adults, and elderly. Non-serious adverse events were reported at comparable rates in the QIV and the TIV vaccine groups. As for solicited systemic adverse events, a slight numerically imbalance was observed also in regard to unsolicited adverse events in the age cohort of children and adolescents 9 to 17 years of age, were non-serious unsolicited adverse events were reported at a higher rate in the TIV compared with the QIV vaccine group. Of note, the sample size in the TIV group was small with 55 subjects compared to 429 in the QIV vaccine group and the observed incidences were within the same range.
In the pooled safety analysis that combined safety data from all studies, a total of 41.5% of subjects in the QIV group of 3 to 8 year old children experienced at least one non-serious unsolicited AE within 28 days following vaccination and 35.6% in the TIV vaccine group. Non-serious unsolicited adverse event rates for the other age groups were 17.5% versus 29.1%, respectively in children and adolescents 9 to 17 years of age, 20.7% versus 19.9%, respectively in adults 18 to 60 years of age, and 14.1% versus 16.7%, respectively in elderly over 60 years of age. The rate of vaccine related non-serious adverse reactions was, beside a slight numerically imbalance in subjects 9 to 17 years of age, comparable across all age and vaccine groups. Unsolicited adverse reactions were reported by 3.3% of

subjects in the QIV group and 2.0% of subjects in the TIV group of children 3 to 8 years of age, 1.4% and 9.1% of subjects, respectively in children and adolescents 9 to 17 years of age, 5.2% and 4.7% of subjects, respectively in adults 18 to 60 years of age, and 3.8% versus 3.4% of subjects, respectively in elderly over 60 years of age. The higher incidence of unsolicited adverse reactions in the TIV vaccine group of 9 to 17 year old subjects was mainly driven by higher incidences of injection site discomfort (0.0% versus 1.8%) and injection site pruritus (0.2% versus 1.8%). Again, this observation is retrieved from the small sample size of 55 subjects in the TIV vaccine group of that age.
The most frequently reported unsolicited related adverse reactions following QIV vaccination across all ages from 3 years occurred in the system organ class of general disorders and administration site conditions (fatigue, injection-site warmth, and injection-site pruritus as leading symptoms), followed by gastrointestinal disorders in the paediatric population (leading symptom diarrhoea), and respiratory, thoracic and mediastinal disorders (oropharyngeal pain) in adults 18 to 60 years of age. In children from 6 to 35 months of age the incidence of non-serious unsolicited AEs was comparable between the QIV (64.3%), the placebo (66.5%) and the pooled TIV (70.6%) vaccine group. The most frequently recorded unsolicited AEs in the QIV vaccine group occurred in the SOCs Infections and Infestations (51.9%), and respiratory, thoracic and mediastinal disorders (13.7%). The incidence and nature of unsolicited non-serious AEs was comparable between the QIV, the placebo and the pooled TIV vaccine group. The majority of unsolicited AEs were of mild or moderate intensity. Grade 3 unsolicited AES were reported for 4.5% in the QIV vaccine group, 4.0% in the placebo, and 6.0% in the pooled TIV vaccine group.

Serious adverse events (SAE)
The number of SAEs was generally low in all age groups and balanced between the QIV and the TIV/Placebo vaccine groups. SAEs were reported by a maximum of 1.6% subjects in the QIV and 1.1% of subjects in the TIV group. Only one SAE was considered to be vaccine related. A 3-year-old female child without relevant medical history developed severe thrombocytopenia 9 days following the first vaccination with QIV. The child recovered within 38 days after onset. Thrombocytopenia following vaccination is a very rare event already known from the TIV and other vaccines (e.g. measles-mumps-rubella vaccines). The event of thrombocytopenia is listed as an uncommon adverse reaction in the Vaxigrip Tetra summary of product characteristic (SmPC) in section 4.8. In study GQM05, one subject experienced a febrile convulsion considered vaccine related by the investigator, but not considered vaccine related according to the sponsor, as the event occurred secondary to an upper respiratory tract infection.

Deaths
A total of eleven deaths were reported in the six clinical trials. None of the death was considered to be vaccine related.

Safety in special populations
The safety of the QIV has not been assessed in immunosuppressed subjects. Inactivated influenza vaccines are considered safe in this population. However, the effectiveness of the vaccine may be reduced. This is indicated as a warning statement in section 4.4 of the Vaxigrip Tetra SmPC.
A total of 986 subjects with underlying chronic illnesses were included into the phase III clinical QIV trials. The safety profile of the QIV in that sub population was not significantly different from that in the overall population. No safety signal was observed. Of note, only subjects with stable diseases that could not interfere with the study contact or completion were included. Patient with acute or severe diseases were not eligible for enrolment.
For ethical reasons, pregnant women are currently excluded from clinical trials. Therefore, no clinical study in pregnant women was performed with the QIV. As a result of inadvertent vaccination, a total of 15 pregnancies were reported in the five clinical QIV trials. The few clinical data collected from these pregnancies do not suggest an adverse effect of the QIV but are too limited for an adequate evaluation of the QIV safety during pregnancy.
However, the increasing data collected from post marketing experience with inactivated influenza vaccines (e.g. registries and spontaneous reports) and from women inadvertently vaccinated during pregnancy in clinical trials indicate that vaccination with inactivated influenza vaccines during pregnancy is not associated with adverse outcomes in pregnant women or their unborn/new born

children. Inactivated influenza vaccination is internationally recommended during any stage of pregnancy and administered to pregnant women.

Safety related to drug-drug interaction

Safety data on concomitant administration of the TIV and a pneumococcal polysaccharide vaccine, Tdap-IPV, and a zoster vaccine in adults and elderly are available. The safety results were comparable when the TIV was administered alone or concomitantly. Data from the paediatric population are missing. It is generally accepted that inactivated vaccines can be administered at the same time as other vaccines, as long as injectable vaccines are administered in different limbs. The SmPC states, that no interaction studies have been performed with Vaxigrip Tetra and that Vaxigrip Tetra can be administered at the same time with other vaccines based on the clinical experience with Vaxigrip.

Discontinuation due to AEs

Adverse events leading to discontinuation were rare. Overall, two subjects discontinued due to an AE following QIV injection. One subject experienced a vaccine related SAE (thrombocytopenia). Another subject was discontinued due to a wrist fracture, which was assessed as not related to the vaccination.

Overall conclusion on clinical safety

The review of the submitted clinical safety data collected in the 6 phase III QIV clinical trials has shown that Vaxigrip Tetra is safe and well tolerated with a safety profile comparable to that of the licensed TIV Vaxigrip which is closely related to Vaxigrip Tetra. No specific safety risks could be identified. Generally, the submitted clinical safety data have not indicated, that the increasing antigen amount due to the additional B strain has any clinically relevant impact on the safety of the vaccine. Thus, it can be expected that the risk-benefit profile of Vaxigrip Tetra is comparable to that of the licensed TIV Vaxigrip. Moreover, a higher benefit due to the second influenza B-strain has to be taken into account.

IV.6 Risk Management Plan

Summary Pharmacovigilance system

The RMS considers that the Pharmacovigilance system, version October 2015' as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimise risks relating to Vaxigrip Tetra. An update of the RMP (Version 5.0) was submitted on 28 July 2017 to include the new indication as of 6 months of age based on GQM05 Clinical Study.

Safety Specification

QIV is indicated for active immunization of adults and children from 6 months of age and older for the prevention of influenza disease caused by the two influenza A virus subtypes and the two influenza B virus types contained in the vaccine.

To address the issue of yearly effectiveness evaluation post marketing the applicant outlined the involvement in two initiatives regarding annual influenza effectiveness assessment. The GIHSN (Global Influenza Hospital surveillance Network) and the Innovative Medicines Initiative (IMI) project called DRIVE (Development of Robust Innovative Vaccine Effectiveness).

According to RMP Version 5.0, no additional Pharmacovigilance studies/activities were deemed necessary.

Table 1 Summary of safety concerns

Important identified risks	None
Important potential risks	Adverse events of special interest: • Anaphylactic reaction • Convulsions (including febrile) • Guillain-Barré Syndrome • Encephalitis/myelitis • Neuritis (including Bell's palsy • Vasculitis • Thrombocytopenia
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 Vaccine efficacy/effectiveness

Enhanced Safety Surveillance

The MAA complies with the Interim Guidance on enhanced safety surveillance for seasonal influenza vaccines (EMA/PRAC/222346/2014), and according to PRAC recommendation to MAHs (EMA/PRAC/775434/2014 and EMA/PRAC/209591/2015). The MAA performs a passive enhanced safety surveillance (EPSS).

Periodic Safety Update Report (PSUR)

With regard to PSUR submission, the MAH should take the following into account:

PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

Common renewal date
5 years after the end of procedure in agreement with CMS.

IV.7 Discussion on the clinical aspects

The available clinical safety and efficacy data are considered adequate to support approval of the QIV Vaxigrip Tetra. Efficacy of the QIV is inferred from the demonstration of non-inferior immune response of the QIV compared with the TIV Vaxigrip manufactured by Sanofi Pasteur. The review of the data has shown that Vaxigrip Tetra is safe and well tolerated with a safety profile comparable to that of the licensed TIV Vaxigrip which is closely related to Vaxigrip Tetra. Most likely, benefits of Vaxigrip Tetra will be higher due to the second Influenza B strain.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The sponsor selected the Irish package leaflet for the testing procedure. The test is based on 2 different testing rounds. The minimum criteria as set out in the readability guideline are fulfilled (2 test rounds, each involving 10 participants). The initial pilot phase checked the questionnaire prior to the user testing. No changes are necessary to ensure that the interviewees can understand the content of the question.
The excellent satisfactory test outcome was demonstrated: the volunteers could find the information as requested and they could show that they can understand the content of the requested response. 100% of the participants demonstrated understanding of the content of the package leaflet. Thus, the readability test is considered acceptable.
No changes of the package leaflet were proposed.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Vaxigrip Tetra (QIV) was developed by Sanofi Pasteur and is indicated for active immunization of adults and children from 6 months of age and older for the prevention of influenza disease caused by the 2 influenza-A virus subtypes and the 2 influenza-B virus types contained in the vaccine. The manufacture, formulation and controls for Vaxigrip Tetra were established based on Sanofi Pasteur's experience with the current licensed trivalent influenza vaccine (TIV) Vaxigrip. The main difference between the 2 vaccines is the addition of a fourth strain, an influenza B-strain, which extends the number of protective influenza strains contained in the vaccine and thereby increases the likelihood of protection against influenza infection with circulating B-strains.
The QIV contains the same HA content per strain; of note, due to the addition of a fourth strain the final antigen content of Vaxigrip Tetra (60 µg HA per 0.5 mL) is higher than that of the licensed TIV (45 µg HA per 0.5 mL). Vaxigrip Tetra has been investigated in a comprehensive clinical trial program. Two clinical phase III trials (GQM01 and GQM04) were conducted with QIV batches from an initial Drug substance manufacturing process with a slightly higher than expected HA content for B strains (mainly in B/Florida). These trials are considered supportive. Four others phase III clinical trials (GQM02, GQM09, GQM11 and GQM05) were conducted with QIV batches from a final commercial DS manufacturing process for which the HA content is in accordance with European Pharmacopoeia requirements for all strains. These trials are considered pivotal. The safety data base for Vaxigrip Tetra is in accordance with applicable guidelines.
The review of the submitted clinical safety data collected in the 6 phase III QIV trials has shown that Vaxigrip Tetra is safe and well tolerated with a safety profile comparable to that of the licensed TIV Vaxigrip which is closely related to Vaxigrip Tetra. The results showed that the safety profile of the QIV is satisfactory and similar to that of the TIV in all age groups. In addition, the safety profile of the QIV is similar to that of Placebo in children aged 6 to 35 months. Overall, adverse reactions were generally less frequent in the elderly than in the adults and in children. This is the case for many vaccines. The most frequently reported adverse reaction after vaccination, in all populations including the whole group of children from 6 to 35 months of age, was injection site pain. The most frequently

reported solicited systemic reactions within 7 days after QIV vaccination in subjects aged 3 years and above were headache, malaise and myalgia. In the subpopulation of children less than 24 months of age, the most frequently reported adverse reaction was irritability and in the subpopulation of children from 24 to 35 months of age it was malaise. No specific safety risks could be identified. Generally, the submitted clinical safety data did not indicate, that the increasing antigen amount due to the additional B strain has any clinically relevant impact on the safety of the vaccine. Thus, it can be expected that the risk-benefit profile of Vaxigrip Tetra is comparable to that of the licensed TIV Vaxigrip. Moreover, a higher benefit due to the second influenza B-strain has to be taken into account.
The immunogenicity of the QIV is inferred from the demonstration of non-inferior immune response of the QIV compared with the TIV manufactured by Sanofi Pasteur in adults and children aged 6 months and older. In addition, the QIV provides evidence of its benefits over those of the TIV by inducing immune responses to two B lineages simultaneously. Moreover, QIV is efficacious in preventing influenza caused by strains similar to the vaccine strains as well as caused by any circulating strains in children aged 6 to 35 months.
Programs are implemented to estimate the effectiveness post-marketing depending on the extent of use of Vaxigrip Tetra.
In summary, it can be concluded that the increasing antigen amount due to the additional B strain does not have any clinically relevant impact on the safety of the vaccine. The safety profile of QIV is considered positive.
Thus, the Vaxigrip Tetra benefit-risk ratio is considered the same as for Vaxigrip in individuals from 6 months of age onwards. Most likely, benefits will be higher due to the second Influenza B strain.

VII. UPDATE ON THE PUBLIC ASSESSMENT REPORT

Procedural steps after finalization of the initial procedure

Date of submission	Procedure Number	Date of Approval	Brief Description
22.07.2016	DE/H/1949/IB/001	05.09.2016	User Testing
18.07.2016	DE/H/1949/IB/002/G	01.11.2016	Scale up of the Filled Product Batch Size; Extension of the Tolerance for the Filtration volume per Surface and the Filtration Flow Rate at Filled Stage.
05.12.2017	DE/H/1949/IB/003/G	08.03.2017	Additional sources of supply for SPF eggs
16.02.2017	DE/H/1949/IB/005/G	20.04.2017	UK Product info: additional distributor
	DE/H/1949/II/006	11.07.2017	Annual Update 2017/2018
28.07.2017	DE/H/1949/II/007	18.12.2017	Extension age indication for children 6-35 months
26.09.2017	DE/H/1949/II/008	07.03.2018	Additional QC testing site Sanofi Winthrop Industrie (Le Trait) for Drug Product
18.10.2017	DE/H/1949/WS/009	01.08.2018	Update of the 3.2.A.2 section "Adventitious Agents Safety Evaluation"
27.10.2017	DE/H/1949/WS/010	27.04.2018	Addition of a new test for mycoplasm by PCR and microarray
22.11.2017	DE/H/1949/001/IA/011/G	22/12/2017	Change of Sanofi Pasteur and Sanofi Pasteur Europe headquarters address
27.06.2018	DE/H/1949/II/013	03.08.2018	Annual Update 2018/2019
13/07/2018	DE/H/1949/001/II/014	17/12/2018	VARIATION TYPE II -

			Replacement of the Haemagglutination Inhibition test (HAI test) by the Single Radial Diffusion test to identify Haemagglutinin (HA) antigen at the Drug Substance stage of the Influenza Vaccine
03/08/2018	DE/H/1949/001/WS/015	07/01/2019	DE/H/xxxx/WS/441 - Type IB grouping of variations: Change in the filtration sequence (step 10) during the Influenza WSL manufacturing process and Description update of the stages 1 and 2 of the Influenza Drug Substance manufacturing process