Unit: Technical Assessment Unit

Public assessment report for biological products

Vaxgrip

Administrative information:

Trade name of the medicinal product:	Vaxigrip
INN (or common name) of the active substance(s):	Haemagglutinin of: A/Darwin/9/2021 (H3N2)-like strain (A/Darwin/9/2021, IVR-228) 15 mcg; A/Victoria/4897/2022 (H1N1) pdm09-like strain (A/Victoria/4897/2022, IVR-238) 15 mcg B/Austria/1359417/2021-like strain (B/Michigan/01/2021, wild type) 15 mcg;
Manufacturer of the finished product	Sanofi Pasteur Parc Industriel d'Incarville 27100 Val de Reuil France
Marketing Authorization holder	Sanofi Winthrop Industrie, 82 avenue Raspail, 94250 Gentilly. - FRANCE;
Applied Indication(s):	Active immunization of adults, including pregnant women, and children from 6 months of age and older, passive protection of infant(s) from birth to less than 6 months of age following vaccination of pregnant women.
Pharmaceutical form(s) and strength(s):	Suspension in prefilled syringe
Route of administration	I.M. or S.C. injection.
Registration track	Fast track
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

I.M.	Intramuscular
S.C.	Subcutaneous
TIV	Trivalent Inactivated Influenza Vaccine
QIV	Quadrivalent Inactivated Influenza Vaccine
WHO	World Health Organization

HA	Haemagglutinin
NA	Neuraminidase
Ph. Eur	European pharmacopeia
MA	Marketing Authorization
MBV	Monovalent Bulk vaccine
CVV	Candidate Vaccine Virus
ERL	Essential Regulatory Laboratories
DS	Drug substance
WFI	water for Injections
DP	Drug Product
PBS	Phosphate Buffered Saline
FBP	Final Bulk Product
FP	Filled Product
DART	Developmental and Reproductive Toxicology
ECG	Electrocardiogram
EDA	Egyptian Drug Authority
EMA	European Medicines Agency
HA	haemagglutinin
HD	Human dose
PSUR	Periodic Safety Update Report
SC	subcutaneous

Table of contents

1. General introduction about the product including brief description of the AI, its mode of action and indications

- The Trivalent Influenza Vaccine is a sterile suspension of influenza virus. The Trivalent Influenza Vaccine contains 3 strains of influenza virus cultivated on embryonated eggs, concentrated, purified, split, inactivated and then diluted in phosphate buffered saline solution to the appropriate concentration.
- The Trivalent Influenza Vaccine is indicated for the prevention of influenza disease caused by the two influenza A virus subtypes and the influenza B virus type contained in the vaccine for: - active immunization of adults, including pregnant women, and children from 6 months of age and older, - passive protection of infant(s) from birth to less than 6 months of age following vaccination of pregnant women. The use of the Trivalent Influenza Vaccine should be based on official recommendations on vaccination against influenza.

2. Quality aspects:

1.2.1 Introduction

As mentioned in the aforementioned section.

1.2.2 Drug Substance (Active ingredient)

- **General information**

The A/H1N1, A/H3N2 and B strains are provided by World Health Organization (WHO) Collaborative Centers and selected in accordance with the annual recommendation (based on antigen variations).

- **Manufacture, process controls and characterization:**
  - **Manufacturer**:

Address 1: SANOFI PASTEUR - MARCY L'ETOILE (MLE) 1541 avenue Marcel Mérieux 69280 MARCY L'ETOILE France
Address 2: SANOFI PASTEUR – VAL DE REUIL (VDR) Parc Industriel d'Incarville Voie De L'Institut
P.O. Box 101 27100 VAL DE REUIL France

  - **Description of Manufacturing Process and Process Controls**

- The Drug Substance (DS) is an aqueous suspension of inactivated, split viral particles that are propagated in embryonated eggs. The Candidate Vaccine Virus (CVV), used to prepare the DS, are selected based on the annual recommendations made by the World Health Organization (WHO) and are supplied by WHO Collaborative Centers, Essential Regulatory Laboratories (ERL) or CVV reassortant labs.
Trivalent Influenza Vaccine (TIV) is composed of a mixture of two A strains (H1N1 and H3N2) and one B strain.

Control of Materials

-A list and specifications of raw materials used in the production of seeds & Monovalent bulk are provided in the MA file.

- **Controls of Critical Steps and Intermediates**

-A flow diagram includes the in-process control measures. All manufacturing steps are considered as critical for the Drug Substance (DS) quality are described in the MA file.

- **Process Validation**

The Process validation is performed to demonstrate that critical processes, operated within established parameters, can perform effectively and reproducibly.

- **Manufacturing Process Development**

- The TIV DS will be manufactured on the same site as for the QIV DS, in the same buildings, as per a manufacturing process that will follow the current validated DS manufacturing process in place for QIV DS. No change will be made to the purification, splitting, inactivation, filtration and dilution phases, to the equipment, to the process parameters, to the In-Process Controls and to the release specification. Moreover, the container closure systems of the QIV and TIV DS are the same.

- **Characterization**

TIV is composed of a mixture of two A strains (H1N1 and H3N2) and one B strain and was developed based on QIV. QIV and TIV DS have exactly the same manufacturing process and Quality Control testing and the manufacturing process of the two vaccines are also the same (except the number of strains) thus the QIV characterization results presented hereafter are applicable to the TIV.

- **Specification**

-The release specification for MVB is presented in the MA file.
-SOPs were provided with the MA file.

- **Batch analysis**

QIV and TIV DS have exactly the same manufacturing process
and the same Quality Control testing; moreover, batches are produced in the same manufacturing buildings. In consequence QIV batch analysis data presented hereafter is applicable to TIV.

Reference Standards or Materials

-For the testing of the potency of the influenza vaccine virus strains in both Monovalent Bulk Vaccine and the Final Lot official reference standard antigens and antisera are used.

- **Container closure system**

Stainless-steel vessels, Plastic Carboys or Single Use Bag System can be used for the storage of the Drug Substance (DS).

- **Stability of drug substance**

Based on available stability data

- ✓ **Approved Shelf Life:** 24 months
- ✓ **Approved Storage Conditions:** 2-8°C

2.2.3 Drug product:

- **Description and Composition of the Drug Product:**

- The Trivalent Influenza Vaccine (TIV), vaccine (split virion, inactivated), is a sterile suspension of influenza virus, containing 15 µg per dose of Haemagglutinin (HA) antigen of two A strains (H1N1 and H3N2) and of one B strain. It is a colorless opalescent liquid presented in a pre-filled syringe that contains one dose of 0.5 ml.

- **Pharmaceutical Development**

- **Components of drug product**

- The Drug Product (DP) consists of the association of three DS and excipient. The excipient is PBS solution containing sodium chloride, potassium chloride, disodium phosphate dihydrate, potassium dihydrogen phosphate and water for Injections (WFI). The three DS are split inactivated influenza viruses corresponding to the three different strains of influenza virions defined each season according to the World Health Organization (WHO) recommendations. The antigen content (Haemagglutinin (HA)) of each influenza virus strain in the final vaccine product is targeted to be 15 µg/dose.

- **Formulation Development**

. The formulation and manufacturing process for the TIV in syringe presentation is based on the licensed Quadrivalent Influenza Vaccine (QIV) in syringe presentation which is a mixture of two strains of influenza virus type A (H1N1 and H3N2) and two strains of influenza virus type B (Victoria lineage and Yamagata lineage) formulated with Phosphate Buffered Saline (PBS) solution.

Manufacturing Process Development

- The manufacturing process development that was done on Quadrivalent Influenza Vaccine (QIV) is applicable to Trivalent Influenza Vaccine (TIV). Except the presence of 2 B strains (Victoria and Yamagata Lineage) in QIV and one B strain for TIV, composition of the two vaccines is the same.

Microbiological Attributes

- The Trivalent Influenza Vaccine (TIV) is a sterile product and is free from preservative. Product sterility and container closure integrity are performed on the Filled Product (FP) during stability studies.

➢ **Compatibility**

- The Trivalent Influenza Vaccine is a ready-to-use formulation; therefore, there is no dilution of the Filled Product.

Manufacture of the drug product:

Description of manufacturing process and process controls along with manufacturers and responsibilities.

➢ **Manufacturer**:

Sanofi Pasteur Parc Industriel d'Incarville 27100 Val de Reuil France.

Process validation and / or evaluation

The Trivalent Influenza Vaccine (TIV) Drug Product (DP) will be manufactured on the same sites as for the Quadrivalent Influenza Vaccine (QIV) DP, as per a manufacturing process that will follow the current validated DP manufacturing process in place for QIV except for the premix of Drug Substances that is not necessary for TIV. No change will be made to the formulation/filling process equipment, process parameters, In-Process Controls and release specification.

➢ **Product specification:**

Release specifications of the Trivalent Influenza Vaccine (TIV) Drug Product (DP) are provided in the MA file.

➢ **Reference Standards or Materials.**

- **Reference antigens and antisera**
- The reference standards that are official reference standards or reference standards calibrated against official reference standards, and chemical reference standards are described for each test.

➢ **Container closure system**

A single dose glass syringe with attached needle, a needle shield and closed with a plunger Stopper or without needle and a tip cap

➢ **Stability of the drug product**

-Based on available stability data,

approved Shelf Life: 12 months

approved Storage Conditions: 2-8°C

3. Non–clinical aspect

The non-clinical development program for Vaxigrip (Trivalent Influenza Vaccine, TIV) is primarily supported by data generated with Vaxigrip Tetra (QIV), given the shared manufacturing platform, formulation principles, and mechanism of action, with the only difference being the absence of one B lineage strain in TIV.

Pharmacology:

In order to demonstrate compatibility between TIV and QIV regarding immunogenicity, the applicant submitted an efficacy study conducted in mice (Study F.RE. QIV002.Ms). Three different batches of QIV containing 15 µg per 0.5 mL of the four strains (A/California/07/2009 (H1N1)pdm09-like virus, A/Texas/50/2012 (H3N2)-like virus, B/Massachusetts/02/2012-like virus and B/Brisbane/60/2008-like virus) and two batches of TIV (one corresponding the commercial TIV vaccine which contains B/Massachusetts strain, and one corresponding to the alternative TIV vaccine which contains B/Brisbane strain) were used. 20 groups of 20 BALB/C ByJ mice each, received 3-fold escalating doses ranging from 1/27 Human Dose (HD) to 1 HD (corresponding respectively to 0.55 µg to 15 µg of HA per strain per dose) of either one of the five batches administered by SC route followed by a booster dose after 21 days.
The functional HI responses measured with the QIV vaccines were similar to those induced by the commercial and the alternative trivalent vaccines except for the B strain that was not included in the TIV vaccine.
A safety pharmacology study (Study number SP0171 PS1404) was conducted to evaluate the effects of QIV on the cardiovascular (blood pressure, heart rate and electrocardiogram (ECG) parameters), respiratory (breathing rate) functions and body temperature in conscious and unrestrained telemetered rabbits over a 24-hour period following one to three intramuscular injections of one human dose of a two-week interval. No premature deaths occurred during the study and there were no adverse clinical signs. Clinical observations were limited to transient erythema and/or edema indicative of a slight local reactogenicity. Blood pressure, heart rate, ECG and breathing rate parameters as well as body temperature, were unaffected by the QIV treatment following each injection. The results of this study are applicable to demonstrate the safety of TIV vaccine as it shares an identical composition except for a missing B strain.

Pharmacokinetics:

Pharmacokinetic studies to demonstrate absorption, distribution, metabolism and excretion of the active ingredients of the TIV vaccines were not performed, this is accepted in accordance with the European Medicine Agency (EMA/CHMP/VWP/457259/2014) and World Health Organization (WHO) guidelines (Technical Report Series Report No. 927: Annex 1, 2005).

Toxicology:

The nonclinical safety evaluation of the QIV included data from a repeat-dose toxicity study and a developmental and reproductive toxicity study that were conducted in rabbits, which were given repeated IM

injections of QIV at the human dose. These studies were previously evaluated for the marketing authorization of QIV. No adverse systemic effects were observed in the nonclinical safety studies. QIV-related effects were limited to minimal and transient local inflammation at the injection site. In addition to the absence of maternal toxicity, the DART study showed no adverse effects on mating performance or fertility, embryo-fetal development and early post-natal development. As in safety pharmacology study, these results also apply to demonstrate the safety of TIV.

Overall conclusion: From the non-clinical point of view, no issues for concern regarding the data submitted for Vaxigrip trivalent vaccine.

4. Clinical aspect:

Clinical Overview

Vaxigrip® is an inactivated, split-virion trivalent influenza vaccine (TIV) intended for active immunization against seasonal influenza caused by two influenza A subtypes (H1N1 and H3N2) and one influenza B strain, in accordance with WHO annual strain recommendations. The vaccine is indicated for adults (including pregnant women) and children from 6 months of age, with passive protection of infants under 6 months following maternal immunization.

The current TIV application is supported by extensive clinical experience and data from Vaxigrip Tetra (QIV), which was approved by the Egyptian Drug Authority (EDA) in March 2020. The TIV and QIV share the same manufacturing platform, formulation principles, and mechanism of action, with the only difference being the absence of one B lineage strain in TIV. No new clinical trials were conducted specifically with the TIV of the current application; therefore, clinical justification relies on immunogenicity, efficacy, and safety bridging from QIV and TIV-initial process data.

Clinical Efficacy and Immunogenicity

* Direct efficacy studies with the TIV of the current application were not conducted. However, clinical efficacy is inferred from:

- Established correlation between HI antibody titers and protection against influenza.
- Demonstrated immunogenic comparability between QIV and TIV-initial process.
- Extensive clinical experience with licensed QIV formulations.

Accordingly, efficacy data generated with QIV are considered applicable and extrapolatable to the TIV of the current application for prevention of seasonal influenza.

* Immunogenicity of the trivalent influenza vaccine is inferred from pivotal clinical studies conducted during the QIV clinical development program (GQM11, GQM02, GQM05), as well as supportive data from study GQM09. These studies demonstrated non-inferiority of immune responses elicited by QIV compared with the TIV-initial manufacturing process for the three shared strains.

The results showed that:

•The immune response against each influenza strain is not affected by the number of strains included in the vaccine (three versus four).
•Changes in the manufacturing process did not impact immunogenicity.
•Comparable hemagglutination inhibition (HI) antibody responses were observed across all age groups for the shared strains.
Based on these findings, the applicant concludes that the TIV of the current application is expected to induce immune responses equivalent to those observed with QIV for the common strains.

Clinical Safety

No new clinical safety studies were conducted for the TIV of the current application. Safety evaluation is based on:
• Clinical safety data from QIV pivotal and supportive studies.
• Post-authorization experience with QIV.
• Non-inferiority of immune responses and identical formulation principles between QIV and TIV, except for the excluded B strain.
Across clinical studies, QIV demonstrated an acceptable safety profile, with adverse events primarily limited to mild and transient local and systemic reactions, consistent with inactivated influenza vaccines. No new or unexpected safety concerns were identified.

Given the similarity in composition and manufacturing process, the safety profile of QIV is considered representative and supportive of the safety of TIV.

Benefit–Risk Conclusion

The benefit–risk balance of Vaxigrip® TIV is considered favorable based on:

• Well-established immunogenicity and inferred efficacy against circulating influenza strains.

• Acceptable and well-characterized safety profile supported by extensive QIV clinical data.

• Significant public health benefit in preventing seasonal influenza, particularly in high-risk populations such as elderly individuals, pregnant women, young children, and patients with chronic diseases.

The exclusion of the B/Yamagata lineage is consistent with recent WHO recommendations and does not negatively impact the overall protective benefit of the vaccine.

Overall Conclusion

In conclusion, although no new clinical trials were conducted with the TIV of the current application, the totality of evidence derived from QIV and TIV-initial process data sufficiently supports the clinical efficacy, immunogenicity, and safety of Vaxigrip® TIV.

5.General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved.