Unit: Technical Assessment Unit

Public assessment report for biological products

Influvac Tetra

Administrative information:

Trade name of the medicinal product:	Influvac Tetra
INN (or common name) of the active substance(s):	Influenza virus surface antigens (inactivated) (haemagglutinin* and neuraminidase) of the following strains: - A/Victoria/4897/2022 (H1N1)pdm09-like strain (A/Victoria/4897/2022, IVR-238) 15 µg HA* - A/Croatia/10136RV/2023 (H3N2)-like strain (A/Croatia/10136RV/2023, X-425A) 15 µg HA* - B/Austria/1359417/2021-like strain (B/Austria/1359417/2021, BVR-26) 15 µg HA* - B/Phuket/3073/2013-like strain (B/Phuket/3073/2013, wild type) 15 µg HA*
Manufacturer of the finished product	Abbott Biologicals B.V. Veerweg 12, NL-8121 AA Olst The Netherlands
Marketing Authorization holder	Abbott Biologicals B.V. C.J van Houtenlaan 36 NL-1381 CP Weesp The Netherlands
Applied Indication(s):	Prophylaxis of Influenza, especially those who run an increased risk of associated complications. Influvac Tetra is indicated in adults and children from 6 months of age.
Pharmaceutical form(s) and strength(s):	Suspension for injection in pre-filled syringe, Haemagglutinin (Per recommended virus strain) 15 µg/0.5 mL
Route of administration	Suspension for intramuscular or subcutaneous injection
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

UFDF	**ultrafiltration/ dia-filtration process step**
FDA	**Food and Drug Administration**
EMA	**European Medicine Agency**
WHO	**World Health Organization**
SC	**Subcutaneous**
IM	**Intramuscular**
MBV	**Monovalent Bulk Vaccine**
SPF	**Specific Pathogen Free**
NA	**Neuraminidase**
HA	**Haemagglutinin**
NH	**Northern Hemisphere**
WSL	**Working Seed Lot**
QIV	**Quadrivalent Influenza Vaccine**
DP	**Drug Product**
DS	**Drug Substance**
DLS	**Dynamic Light Scattering**
QBV	**Quadrivalent Bulk Vaccine**
TBV	**Trivalent Bulk Vaccine**
ULDPE	**Ultra Low Density Poly Ethylene**
FBP	**Final Bulk Product**
UK	**United Kingdom**
USA	**United States of America**
USP	**United States Pharmacopoeia**

Table of contents

1. **General introduction about the product including brief description of the AI, its mode of action and indications.**
   - Quadrivalent Influenza Vaccine (Surface Antigen, Inactivated) is a clear, aqueous suspension packed in pre-filled syringes with/without needle (glass, Type I), each containing 0.5 mL for IM or deep S.C. administration.
   - The vaccine is a sterile, clear, aqueous suspension that contains predominantly haemagglutinin and neuraminidase antigens of four strains of influenza virus in phosphate buffered saline.

2. **Quality aspects:**

2.2.1 Introduction

As mentioned above in the general introduction.

2.2.2 Drug Substance (Active ingredient)

- **General information**

International Name: " Quadrivalent influenza vaccine (Surface antigen, inactivated)".
European Pharmacopoeia name: "Influenza vaccine (Surface antigen, inactivated) The Ph. Eur refers to Monovalent Pooled Harvest in Monograph 0869, Influenza vaccine (surface antigen, inactivated).
General properties:
Influenza vaccine is composed of egg-grown. inactivated, surface influenza antigens of four strains of influenza virus: two A strains and two B strains. The strain information is updated annually as recommended by the World Health Organization for the Northern Hemisphere.

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

    Monovalent Bulk Vaccine and Final Bulk Vaccine are manufactured by:
    Abbott Biologicals B.V.,
    C.J van Houtenlaan 36
    NL-1381 CP Weesp
    The Netherlands

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

All the manufacturing process steps of the seasonal influenza vaccine monovalent bulks are covered & submitted in MA file

- **Control of Materials.**

Eggs:
• Embryonated SPF chickens' eggs are used for the propagation of virus seed stocks and Embryonated chickens' eggs from healthy flocks are used for routine production.
• Master Seeds and Working Seeds are prepared by successive passages of the original strain (Primary Seed Virus) in embryonated Specific Pathogen Free (SPF) eggs according to the WHO and Ph.Eur.

guidelines where a certificate of conformity with Ph. Eur. is provided with each delivery of eggs and is attached to the release package of the seed materials.

Raw Materials:

• All raw materials of synthetic origin used to prepare the biological substances are of non-animal origin and comply with the European Pharmacopoeia.

• All raw materials are tested according to the relevant monographs using the most stringent standard (method or limit) that is compliant with the pharmacopeia requirements. Control of **Viral Seeds:**

All Quality Control tests on the viral strains are performed by the respective Word Health Organization (WHO)

Collaborative Centers. Compliance with the specifications of the WHO Collaborative Center is certified by a certificate of

analysis accompanying each virus at delivery.

- **Controls of Critical Steps and Intermediates.**

The manufacturing steps are considered critical for the Drug Substance (DS) quality and In-Process Control Tests are applied:

A flow diagram includes the in-process control measures. The in-process controls generally describe the two critical aspects of the Monovalent Bulk Vaccine. These are the microbial contamination levels and the retention of the active principle, haemagglutinin, through the purification process. Monitoring the haemagglutinin content permits the success of the various steps in preserving the active principle in the retained portion to be assessed.

- **Process Validation**

• The critical process parameters defined for the Influenza monovalent bulk manufacturing process are provided with their operating ranges.

• Critical process parameters are either validated or, alternatively, the performance of the production step in which these critical parameters operate, will be controlled on each batch produced in order to guarantee the production-step robustness.

• The demonstration of process consistency for at least three consecutive batches, which must show compliance with the pre-established quality standards was carried out.

• The consistency batches met all in-process control limits for the quality decision test as well as the release acceptance criteria for monovalent bulks.

- **Manufacturing Process Development.**

-The manufacture of influenza vaccine (surface antigen, inactivated) has been performed for many years. During this period the manufacturing process has been developed, refined, and is continually reevaluated to optimize the process and incorporate the new strains of influenza virus. This has resulted in the improvements made to the production process described below:

1. The strain-dependent steps are validated annually for each new strain of influenza virus. The batch analysis results are presented annually.

2. The key steps are validated for each new strain of influenza virus. Drug Substance Critical Quality Attributes and Control Strategy and Supportive Data for Holding Times of the Drug Substance Manufacturing Process are described and satisfactory.

- **Characterization.**

Elucidation of Structure and Other Characteristics:
The active principle, the Monovalent Bulk, contains the haemagglutinin and neuraminidase antigenic activity specified for one of the influenza virus strains as recommended by WHO/CHMP. The primary seed virus is received with a certificate of analysis specifying the strain of virus and its characteristics.
Impurities:
The process related residuals that potentially could be present in the purified monovalent bulks are clearly described in the MA file and are removed during the purification steps.

- **Specification**

Assays involved in control of drug substance are performed according to approved control procedures that describe the main steps in a procedure. The specification for each test is stated in the MA file and performed on the first three DS batches manufactured from any new working seed lot.

- **Analytical Procedures.**

Analytical procedures used for testing the Quadrivalent Influenza Vaccine Drug Substance (DS) are described in the MA file.

- **Reference Standards or Materials.**

The reference standard antigens and antisera are provided by the WHO and CHMP designated laboratories. The European manufacturers usually receive the reference standards from NIBSC (UK), CBER (USA) or TGA (Australia).

- **Container closure system**

The sterile filtrated influenza vaccine (surface antigen. inactivated) Monovalent Bulks are stored for limited periods of time at 2 to 8°C in stainless steel containers or disposable bags.

- **Stability of drug substance**

Every year, stability studies are performed on representative monovalent bulk batches of the production for each new strain. These studies are performed in realtime/real-temperature conditions (i.e. normal conditions: 18 months at +5°C ± 3°C) and in accelerated conditions (6 months at +25°C + 2°C). In conclusion, all results obtained after 18 months of storage at +5°C ± 3°C conform to acceptance criteria and are in the expected trend for the three studied batches. three DS batches issued from each strain are included in an initial stability program corresponding to study under real conditions of storage (18 months at +5°C ± 3°C) and under accelerated conditions (6 months at +25°C ± 2°C).
In conclusion, results of the stability studies so far, performed on strains used until NH 2024/2025 are convenient.

2.2.3 Drug product:

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

Quadrivalent Influenza Vaccine QIV (Surface Antigen, Inactivated) is a clear, aqueous suspension packed in pre-filled syringes each containing 0.5 mL. The vaccine is a sterile. clear, aqueous suspension that contains predominantly haemagglutinin and neuraminidase antigens of four strains of influenza virus in phosphate buffered saline.

- **Pharmaceutical Development including brief description on Components of drug product.**

Drug substance: The Drug Product (DP) consists of the association of four DS and excipient. The four DS the surface antigens, haemagglutinin and neuraminidase, of the enveloped influenza viral strains which are specified annually for the Final Lot by WHO and CHMP or AIVC for the Northern or Southern Hemisphere, respectively.

Excipients: The DP contains salts and buffering agents to preserve the antigenic potency by maintaining its tonicity and pH.

- **Formulation Development**

the formulation of quadrivalent influenza vaccine (surface antigen, inactivated) (QIV) was developed by adding a B-strain to the trivalent influenza vaccine (surface antigen, inactivated) (TIV). The auxiliary components remain the same. The development includes:

Clinical trial formulae for the clinical studies of QIV, a composition with 4 relevant vaccine strains was used, depending on the season.

- Overages

Influenza vaccine, surface antigen, inactivated, is described in the Ph. Eur. 0869. The content of haemagglutinin for each strain present in the vaccine is 15 µg / dose, unless clinical evidence supports the use of a different amount, and the confidence interval (P=0.95) of the assay is between 80% to 125% of the estimated content. The lower confidence limit (P=0.95) of is not less than 80 per cent of the amount stated on the label for each strain (12 ug/dose).

- Physicochemical and Biological Properties

The Final Bulk, contains the haemagglutinin and neuraminidase antigenic activity specified for four influenza virus strains as recommended by WHO and CHMP/AIVC.

- **Manufacturing Process Development.**

For the formulation of QIV, only one additional strain is included. As a consequence, more product related compounds in particular proteins (HA and proteins other than HA) will be present in the Final Bulk and Final Lot of QIV. The auxiliary components remain the same. The matrix, formulation and density of Trivalent Bulk Vaccine (TBV) and Quadrivalent Bulk Vaccine (QBV) are the same. Therefore, the production process and contact materials remain the same.

- **Container closure system and their compatibility.**

A syringe is used as container closure system / administration device for influenza vaccine (surface antigen, inactivated). The container closure components which are in contact with the vaccine are a glass barrel type I and a plunger of rubber. The suitability of the container closure system was studied for the storage, transportation (shipping), and use of the drug product. And the results were satisfactory.

- **Microbiological Attributes.**

The suitability of the container closure system in the prevention of microbial contamination has been investigated. The results of the stability trials demonstrate that the integrity of the seals is maintained during storage.

  - **Compatibility.**

Influenza vaccines are not administered neither in the same administration apparatus as other pharmaceutical preparations at the same time nor other diluents, thus negating the risk of pharmaceutical interaction.

- **Manufacture of the drug product:**
  - Description of manufacturing process and process controls along with manufacturers and responsibilities.
  Abbott Biologicals B.V.
  Veerweg 12,
  NL-8121 AA Olst
  The Netherlands
  - Process validation and / or evaluation.

The overall process validation for the production of Quadrivalent Influenza Vaccine (QIV) assesses the critical steps to ensure adequate quality assurance of the drug product.

- **Product specification:**
  - Description of the product specifications (state the reference whether compendial or in-house) and the excipients (mention excipient specifications) as well.
  - **Characterization of impurities.**

Drug Substance Related Impurities: there is no additional impurity due to the manufacturing processes of the Final Bulk Vaccine (FBV) and FP.

Reference Standards or Materials.

The reference standard antigens and antisera are provided by the WHO and CHMP designated laboratories. The European manufacturers usually receive the reference standards from NIBSC (UK), CBER (USA) or TGA (Australia).

- **Container closure system.**

1-Final Bulk Vaccine:

The container closure system used for the storage of the Final Bulk Vaccine (FBV) at +5°C ± 3°C are disposable bags.

2-Filled Product:

The influenza vaccine (surface antigen, inactivated) is filled in 1 mL Long syringes. The vaccine is kept in a type I glass syringe barrel with or without needle. The glass barrel is closed at one end with a rubber plunger and at the other end with a rubber tip cap or needle.

- **Stability of the drug product.**

1 Stability Summary and Conclusion

- Stability study was performed on three Quadrivalent Bulk Vaccine batches. From this study is was concluded that the Final Bulk is stable for three months at 5 ± 3°C. - All formulations are tested for at least 12 months, at the recommended storage condition of 5°C (5 ± 3°C) and under accelerated conditions, temperature of 25°C (25 2°C). In the stability studies for quadrivalent influenza vaccine the results for the other parameters that have been studied were all within the specifications and therefore support the shelf-life claim. The data obtained with storage at 25°C show that short excursions at these temperatures will not immediately lead to a decrease of the HA content in the product. From the data it is concluded that occasional exposure to higher temperatures up to one month does not affect the stability of the product.

3. **Non –clinical aspect:**

According to the Guideline on Influenza Vaccines Non-clinical and Clinical Module (EMA/CHMP/VWP/457259/2014), non-clinical studies are not required to support marketing authorization of seasonal strains updates.

4. **Clinical aspect:**

- **Clinical Efficacy Conclusion**

The clinical efficacy of Influvac Tetra (quadrivalent influenza vaccine, QIV) is supported by extensive experience with Abbott's trivalent influenza vaccine (TIV), which has been in use for over 30 years. Both B strain lineages Yamagata and Victoria have been alternately included in TIV formulations, and their immunogenicity and safety profiles have been well characterized. The only substantive change in QIV is the inclusion of both B lineages in a single formulation, with no other modifications to the manufacturing process or antigen content (15 µg per strain).
Two pivotal studies INFQ3001 in adults and INFQ3002 in children and adolescents demonstrated that QIV elicited noninferior immune responses to all shared strains compared to TIV, with no evidence of immunological interference. In adults and elderly participants, QIV induced higher antibody responses to the additional B strain not present in TIV, and all serological parameters (seroprotection, seroconversion, and mean fold increase) exceeded the criteria set by the CHMP for acceptable immune responses. Virus neutralization assays confirmed the presence of functional antibodies.
In children and adolescents (3–17 years), QIV also met noninferiority criteria for all strains and showed superior responses to the additional B strain compared to cross-reactive responses in TIV. The immune responses were consistent across age groups and priming status, with comparable HI, VN, and NI titers between QIV and TIV for shared strains.
Study INFQ3003 in children 6 – 35 months of age demonstrated absolute efficacy of QIV in the prevention of symptomatic influenza infection compared with a non-influenza vaccine.

- **Clinical Safety Conclusion**

The safety and reactogenicity profiles of Influvac Tetra were comparable to those of the trivalent formulation. In adults and elderly subjects, the incidence of treatment-emergent adverse events (TEAEs) was low and similar between QIV and TIV groups (4.8% vs. 3.6% in adults; 3.8% vs. 2.7% in elderly). Most TEAEs were unrelated to vaccination, and no adverse events led to study discontinuation. Local and systemic reactions were generally mild to moderate in severity and resolved within 1 to 3 days.
In children and adolescents, the incidence of TEAEs was also comparable between QIV (18.9%) and TIV (22.6%) groups. The most common reactions such as headache and fatigue were mild or moderate and transient.
In children 6 – 35 months of age similar TEAE reporting rates were observed between QIV and non-influenza vaccine vaccination groups.
The addition of a second B strain in QIV did not increase reactogenicity or alter the overall safety profile. Local and systemic reactions were generally mild to moderate in severity and resolved within 1 to 3 days.

- **Overall Conclusion**

Influvac Tetra demonstrates a favorable benefit-risk profile, offering broader protection against seasonal influenza by including both B strain lineages without compromising safety or immunogenicity. The vaccine meets established regulatory criteria for efficacy and safety in both pediatric and adult populations, supporting its use as a reliable quadrivalent influenza vaccine for routine immunization.

5. General Conclusion and Recommendations if any: