EDA Assessment Report for Biological Medicinal Product

(Scientific Discussion)

Influvac TIV

Date: August 2025

Unit: Technical Assessment Unit

Public assessment report for biological products

Influvac TIV

Administrative information:

Trade name of the medicinal product:	Influvac
INN (or common name) of the active substance(s):	Haemagglutinin of: • A/Victoria/4897/2022 (H1N1) pdm09-like strain (A/Victoria/4897/2022, IVR-238) 15 µg • A/Thailand/8/2022 (H3N2)-like strain (A/California/122/2022, SAN-022) 15 µg • B/Austria/1359417/2021-like strain (B/Austria/1359417/2021, BVR-26) 15 µg
Manufacturer of the finished product	Abbott Biologicals B.V.C.J van Houtenlaan 36, NL-1381 CP Weesp- 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 is indicated in adults and children from 6 months of age.
Pharmaceutical form(s) and strength(s):	surface antigens haemagglutinin and neuraminidase; 0.5 ml of the vaccine suspension for injection contains 15 microgram of the antigen haemagglutinin of each recommended virus strain.
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
CTD	Common technical document
SOPs	Standard operating procedures

WHO	World Health Organization
CHMP	Committee for Medicinal Products for Human Use
AIVC	Australian Influenza Vaccine Committee
HA	Haemagglutinin
NA	Neuraminidase
NIBSC	National Institute for Biological Standards and Control
UK	United Kingdom
SPF	specific pathogen-free
MSV	master seed virus
WSV	working seed virus
Ph. Eur	European pharmacopeia
MA	Marketing Authorization
MBV	Monovalent Bulk vaccine
PVDF	polyvinylidene fluoride
SDS-PAGE	Sodium Dodecyl-Sulfate Polyacrylamide Gel Electrophoresis
TGA	Therapeutic Goods Administration
ULDPE	Ultra Low-Density Polyethylene
CBER	Center for Biologics Evaluation and Research
PSV	primary seed virus

Dossier initial submission and evaluation process.

- The product was submitted for registration via 343/2021 ministerial decree.
- The dossier evaluation by the registration administration units was started on 5.6.2024 then new strain was submitted on 19.2.2025 after providing all the required documents according to the Checklist for documents of new biological products registration file.
- Full CTD along with detailed SOPs were provided.

Table of contents

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

-The Influenza Vaccine (Surface Antigen, Inactivated) is a sub-unit vaccine and contains the surface antigens haemagglutinin and neuraminidase; 0.5 ml of the vaccine suspension for injection contains 15 micrograms of the antigen haemagglutinin of each recommended virus strain.
-The vaccine presentation is a pre-filled single-dose syringe and administered through an intramuscular or deep subcutaneous injection.
-The antigens stimulate the production of antibodies against the specified influenza strains; the vaccine is therefore used for the prophylaxis of influenza, especially in those who run an increased risk of associated complications.
-The production of influenza vaccines was started in 1947. Egg derived influenza vaccines have been developed and improved by the manufacturer during the intervening years.
-The finished product contains one or more active drug substances, from strains as specified annually by WHO/CHMP (EU) (Northern Hemisphere) or WHO/AIVC (AU) (Southern Hemisphere); in recent years three strains of influenza virus antigens have been specified.
-Each drug substance is a Monovalent Bulk Vaccine, containing haemagglutinin and neuraminidase of one virus strain.
-All the drug substances involving viruses propagated on eggs are manufactured and controlled in the same way and stored in the same types of containers.

2. Quality aspects:

1.2.1 Introduction

As mentioned in the aforementioned section.

1.2.2 Drug Substance (Active ingredient)

- **General information**

-The protein structure of influenza haemagglutinin (HA) is primarily defined by its amino acid sequence and this sequence is strain specific. Further, the structure of an HA protein is also determined by its strain specific glycosylation pattern.
-The biological activity is mainly related to the antigenic or immunoreactive content of the haemagglutinin functional protein.
-This parameter is quantified through a validated immunochemical method (SRD). Next to that, the presence of tertiary and quaternary structures of neuraminidase (NA) as a functional enzyme is also a factor to consider. It should be noted that this information is updated annually with the updates recommended by WHO.

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

Abbott Biologicals B.V.
C.J. van Houtenlaan 36
1381 CP Weesp
The Netherlands

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

-The virus strain is supplied as a primary seed virus by the NIBSC (National Institute for Biological Standards and Control, Potters Bar, UK), or by another designated WHO laboratory.
-This is propagated in embryonated SPF (specific pathogen-free) hens' eggs to generate a master seed virus (MSV). The working seed virus (WSV) is generated by the propagation of the MSV in embryonated SPF hens' eggs. The maximum number of passages in eggs from the primary seed virus to WSV is within the defined maximum of Ph. Eur. monograph 0869.
-The production process of each monovalent virus bulk, along with the in-process control tests, is well represented in the MA file.

- **Control of Materials**

-A list and specifications of raw materials used in the production of seeds & Monovalent Bulk Vaccine are provided in the MA file.
-The WHO collects samples of influenza viruses in the field, the viruses are reviewed and selected.
-Viruses are passaged through eggs by the WHO specified laboratories. The primary seed virus is supplied to the manufacturer by a WHO designated laboratory.
The primary seed virus is used to produce the master seed virus (MSV) and working seed virus (WSV). The WSV is controlled in accordance with the requirements of Ph. Eur. monograph 0869.

- **Controls of Critical Steps and Intermediates**

-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**

- **Validation of the active substance:**

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-Process validation and comparability were executed successfully with three consecutive full size MBV batches as per the provided validation report.

❖ **Validation of the inactivation step:**

During the process validation study, three consecutive full size MBV batches were produced from different strain (A/H3N2, A/H1N1, B strain) to cover strain dependent aspects on both inactivation kinetics and product quality.
The process validation was completed successfully.

❖ **Validation of the Filtration of Allantoic Fluid:**

-The provided validation report demonstrated that filtration does not result in substantial losses of the virus content.

➢ **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.

➢ **Characterization**

-Influenza vaccine (surface antigen, inactivated) MBV is primarily composed of the two influenza viral surface antigens HA and NA.
-The master and working seed viruses are produced from the primary seed virus and are analyzed to confirm the identity of the haemagglutinin and neuraminidase, and the infectivity, using specific antisera and antigen reactions.
-For Monovalent Bulks, the haemagglutinin identity and assay are determined using the single radial diffusion assay. The identity of the neuraminidase in the first three batches of each Monovalent Bulk Vaccine produced from each batch of working seed virus is determined, as required by Ph. Eur. monograph 0869, using specific antisera and antigen reactions.
--A validation showed that the level of residual gentamicin is below the limits of detection.

➢ **Specification**

-The release specification for MBV comprises tests for identity, purity and impurities, quantity, potency, microbiological attributes and general attributes.
-Some analytical procedures are in compliance with the European Pharmacopoeia and other ones are in-house which are fully validated.
-SOPs were provided with the MA file.

- **Batch analysis**

-Batch analysis results of the first three MBVs are provided which comply with the predetermined specifications.

- **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 specific reference standard antigens and antisera are used, which are provided by WHO or one of the designated laboratories, such as NIBSC (UK) or TGA (AU).
-The reference standards (which are the reference standards for the (SRD) potency assay) are closely related to (or: even dependent on) the annual virus strains.
-As the strain composition is changing each influenza season, the reference standard details are included in the SRD assay validation report submitted each season as part of annual strain updates

- **Container closure system**

-The sterile filtrated influenza vaccine (surface antigen, inactivated) Monovalent Bulks are stored at 2 to 8°C in glass, stainless steel, or flexible Ultra Low Density Polyethylene (ULDPE) containers.
-The single use bags comply with USP <661>, <87> and <88> and meets all requirements of Ph. Eur.3.1.5

- **Stability of drug substance**

Based on available stability data

- ✓ **Approved Shelf Life:**
  15 months

- ✓ **Approved Storage Conditions:**
  Store at (5±3°C)

2.2.3 Drug product:

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

-Influenza vaccine (surface antigen, inactivated) complies with Ph. Eur. monograph 0869.
-The vaccine is a sterile, clear, aqueous suspension that contains predominantly hemagglutinin and neuraminidase antigens of three strains of influenza virus in phosphate buffered saline packed in 0.5 mL pre-filled syringes.

-Each year the particular strains recommended for the next influenza season for the northern hemisphere are established by the World Health Organization and the CHMP (EU).
-The potency of the vaccine is expressed as the concentration of the hemagglutinin protein.
-The target concentration is 15 µg hemagglutinin per strain per 0.5 ml, according to Ph. Eur. monograph 0869.
-It was provided for the strain composition and the theoretical formula per dose, for the 2024/2025 Northern Hemisphere influenza season.

- **Pharmaceutical Development**

- **Components of drug product**

-The manufacture of the finished Product involves blending and diluting the drug substance with a buffer to produce the Final Bulk Vaccine (FBV). The Final Bulk Vaccine is filled into syringes.
-The product contains the quantities of the surface antigens, predominantly haemagglutinin and neuraminidase, of the influenza viral strains, which are specified annually by WHO/ CHMP (EU).

- **Formulation Development**

-A 0.25 mL dosage can be administered from the syringe filled with 0.5 mL by using the 0.25 mL marking on the syringe.
-bBatches of MBV used for clinical batches were taken from MBVs manufactured according to the production process as described in the dossier, only the Final Bulk Vaccine mixing volume has been smaller.
-Influenza vaccine (surface antigen, inactivated) is produced and released with an overage to ensure that the content will remain within Ph. Eur. specifications until the date of expiry.

- **Manufacturing Process Development**

-The manufacturing process for the marketed egg-derived products has been employed for many years. The required quantities of the Monovalent Bulk Vaccines are combined and diluted with the buffer to yield, the Final Bulk containing the specified quantities of the antigens. The Final Bulk Vaccine is filled into sterile syringes.
-0.22 µm filtration of the Final Lot prior to filling into syringes is implemented
-The use of disposable containers is supported by stability studies.

- **Microbiological Attributes**

-The suitability of the container closure system in the prevention of microbial contamination has been investigated during regular annual stability studies. Initial stability data demonstrate that the integrity of the seals is maintained during storage

- **Compatibility**

-Influenza vaccines are not administered in the same administration apparatus as other pharmaceutical preparations, thus negating the risks of pharmaceutical interaction.

Manufacture of the drug product:

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

- **Manufacturer**:

The final bulk is manufactured at Abbott Biologicals B.V.
C.J. van Houtenlaan 36
1381 CP Weesp
The Netherlands

While filling of final lot into syringes, secondary packaging,labeling and batch release is performed at Abbott Biologicals B.V.
Veerweg 12
8121 AA Olst
The Netherlands

- **Control of critical steps and intermediates**

  The manufacturing process is controlled through critical process parameters, in process testing and release testing. A summary of the critical process parameters and tests for the finished product is provided in the dossier.

- **Process validation and / or evaluation**

The purpose of drug product process validation including final bulk formulation and filling process is to demonstrate the consistency and reproducibility of the manufacturing processes for drug product. The manufacturing process results of all test items were met with the predefined acceptance criteria. According to the results, this process validation provided consistency and reproducibility of manufacturing process.

- **Release testing**

-All release test results performed on the Final Lot batches comply with the specifications.

- **Product specification:**

-Specifications proposed for release and stability testing of the finished product comply with European Pharmacopoeia
-Detailed SOPs validation protocols & reports are provided for the in-house methods
-The specifications include general characteristics, biological& general safety tests, potency &identity tests
-Justification of the drug product specifications at the release and during stability studies are provided.
-The excipients are purchased in compliance to the Ph. Eur. specifications. A test certificate accompanies each batch supplied to guarantee compliance with the specifications.

- **Reference Standards or Materials.**

- **Reference antigens and antisera**

-The reference standard antigens and antisera are provided by WHO- Collaborating Centers: NIBSC (UK) or TGA (Australia).

- **Control authority batch release**

Each batch manufactured and released by the manufacturer is subject to Official Control Authority Batch Release as described in EC Directive 2001/83/EC as amended. This release is based on examination and approval of the manufacturer's production and test protocols and on satisfactory test results.

- **Container closure system**

- **Container closure system of the final bulk**

-For storage of Final Bulk, disposable flexible bags are used; multiple-use stainless steel containers may be used as a back-up scenario. The bags are sterilized by γ-irradiation.

- **Container closure system of the final lot**

The influenza vaccine (surface antigen, inactivated) is filled in 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.
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- **Stability of the drug product**

-Based on available stability data,

- ✓ **approved Shelf Life:** 12 months
- ✓ **approved Storage Conditions:**
- Store at (2 -8°C)
- Store in a refrigerator
- Do not freeze.
- Store in the original package in order to protect from light.
- Shake before use

- **Adventitious agents:**

-The influenza vaccine is a seasonal influenza vaccine. The current formulation (i.e., without a preservative) has been marketed since 2004. Influenza
vaccine (surface antigen, inactivated) is manufactured according to Ph. Eur. monograph 0869 and has a well-established safety and efficacy profile in all human populations, including children older than 6 months of age.
- Complementary measures have evolved to control the potential virus contamination to assure the viral safety of the product.

-A periodic review of the risk assessment is performed including new information about on current and emerging viruses and mycoplasmas.The

3.Non–clinical aspect:

-The Common Technical Document (CTD) Module 4 (Non-clinical) was not submitted by the applicant for this product based on the fact that this product is considered as safe and well-established.
-At the time of renewing the authorization of Influvac (trivalent) in The Netherlands, in the context of the EU Mutual Recognition Procedure (MRP) in 1997, it was decided by the European Heads of Medicine Agencies that seasonal inactivated influenza vaccines could be exempted from conducting non-clinical studies based on the fact that they were well-established, widely used products with a favorable benefit-risk profile.
Further, because seasonal influenza vaccines are low-dose products intended for once-yearly administration, it was considered that repeated-dose toxicity studies would be not necessary.

4.Clinical aspect:

- **Clinical Pharmacology conclusion:**

Clinical pharmacokinetic studies are not requested as part of the evaluation of vaccines, as indicated by the CHMP “Guideline on Clinical Evaluation of New Vaccines” (EMEA/CHMP/VWP/164653/2005). The constituents of the influenza vaccine are phagocytosed at the site of injection. Therefore, specific interaction or pharmacokinetic studies have not been carried out in man. Regarding pharmacodynamic properties, seroprotection is generally obtained within two to three weeks. The duration of post-vaccination immunity to homologous strains or to strains closely related to the vaccine strains varies but is usually 6-12 months.

- **Clinical efficacy conclusion:**

▪ The Influenza Vaccine (Surface Antigen, Inactivated) is a sub-unit vaccine and contains the surface antigens haemagglutinin (HA) and neuraminidase (NA). The antigens stimulate the production of antibodies against the specified influenza strains; the vaccine is therefore used for

the prophylaxis of influenza, especially in those who run an increased risk of associated complications (elderly and subjects of any age at risk of serious complications and mortality after influenza infection). Trivalent influenza vaccine (surface antigen, inactivated) is a mixture of two influenza A strains and one influenza B strain from either Yamagata or Victoria lineage.

- From the scientific literature, clinical efficacy of trivalent inactivated influenza vaccine in clinical trials has been reported to be 59% (95% CI 51-67%) in adults aged 18-65 years, with significant seasonal variability. Overall, the influenza vaccine produced a consistent and adequate response; the average seroprotection rates were over 80% for adults and over 70% for the elderly, which are well above the minimum CHMP (EU) requirement.
- The strain composition of the vaccine is adapted yearly to the recommendation of the WHO and CHMP (EU), in accordance with the changes in the prevalence of the circulating influenza virus strains. For trivalent vaccines for use in the 2024-2025 northern hemisphere influenza season, **WHO recommends the following:**
- Egg-based vaccines: an A/Victoria/4897/2022 (H1N1) pdm09-like virus, an A/Thailand/8/2022 (H3N2)-like virus and a B/Austria/1359417/2021 (B/Victoria lineage)-like virus. There have been no confirmed naturally occurring B/Yamagata lineage virus detections after March 2020.
- According to the recommendation of WHO from September 2023, the opinion of the WHO influenza vaccine composition advisory committee that the B/Yamagata lineage antigen should be excluded from influenza vaccines as it is no longer warranted. National or regional authorities should make decisions regarding the transition to trivalent influenza vaccines in their jurisdictions.
- Over a period of more than 30 years including more than 10,000 subjects exposed to trivalent influenza vaccine (surface antigen, inactivated) in clinical trials since 1982, trivalent influenza vaccine (surface antigen, inactivated) consistently induced a reliable immune response in both the adult and elderly age groups; the average seroprotection rates were over 80% for adults and over 70% for the elderly subpopulation. Overall, the influenza vaccine produced a consistent and adequate response; the average seroprotection rates were over 80% for adults and over 70% for the elderly, which are well above the minimum CHMP (EU) requirement.

➢ **Clinical safety conclusion:**

- Until 2014, it was a requirement in EU to conduct yearly annual update clinical studies to demonstrate safety and tolerability of the vaccine with updated strain composition. Study results demonstrated the product had favorable safety profile and complied with the recommendation of the WHO and the CHMP (EU) (northern hemisphere) or the AIVC (AU) (southern hemisphere) for the particular season.

-Section 4.8 of the SPC for influenza vaccine (surface antigen, inactivated) lists the adverse events as reported in the (annual) Periodic Safety Update Reports.

➢ **Clinical Immunogenicity conclusion:**

- Immunogenicity of vaccine was measured as apart of efficacy results.

➢ **Benefit/ Risk discussion:** In conclusion the overall benefit/risk of Influvac**,** suspension for injection 0.5ml, is favorable in prophylaxis of influenza, especially those who run an increased risk of associated complications. Influvac is indicated in adults and children from 6 months of age, the use of Influvac should be based on official recommendations.

5.General Conclusion and Recommendations if any:

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