EDA Assessment Report for Biological Medicinal Product

(Scientific Discussion)

GC Flu Quadrivalent

Date: November 2024

Unit: Technical Assessment Unit

Assessment report

GC Flu

Administrative information:

Invented name of the medicinal product:	GCFLU Quadrivalent pre-filled syringe inj. Influenza vaccine (split virion. Inactivated)
INN (or common name) of the active substance(s):	Each 1 Pre-Filled Syringe (0.5 ml) contains: • Purified Influenza Virus Antigen (Split Virion, inactivated) Type A [A/Victoria/2570/2019 IVR-215 (A/H1N1)] ----------15 µg • Purified Influenza Virus Antigen (Split Virion, inactivated) Type A [A/Darwin/9/2021 SAN-010 (A/H3N2)] ----------15 µg • Purified Influenza Virus Antigen (Split Virion, inactivated) Type B [B/Austria/1359417/2021/BVR-26 (B/Victoria Lineage)] -- 15 µg • Purified Influenza Virus Antigen (Split Virion, inactivated) Type B [B/Phuket/3073/2013 (B/Yamagata Lineage)] ----------15 µg
Marketing Authorization holder	GC Biopharma Corp., 40, Sandan-gil, Hwasun-eup, Hwasun-gun, Jeollanam-do. Republic of Korea
Applied Indication(s):	Prophylaxis against influenza caused by influenza A subtype viruses and type B viruses in persons aged 6 months and older.
Pharmaceutical form(s) and strength(s):	Solution for IM injection in Pre-filled Syringe
Route of administration	I.M injection
Approved pack(s)	Carton box containing 10 prefilled syringes (0.5ml), consists of colorless or light brown, transparent, no air bubble glass (Type I Borosilicate) syringe barrel, with attached one disposable stainless-steel needle, transparent

	polystyrene plunger rod, gray chlorobutyl rubber stopper, a blister package and insert leaflet.

List of abbreviations

I.M	intramascular
CTD	Common technical document
SOP	Standard operating procedure
MFDS	Ministry of Food and Drug Safety
WHO	World health organization
DS	Drug substance
Ph.Eur	European Pharmacopoeia
NIBSC	The National Institute for Biological Standards and Control
GC3110A	Quadrivalent influenza vaccine, study item
CQA	critical quality attributes
PFS	pre-filled syringes
QIV	quadrivalent, inactivated influenza split vaccine
ADR	Adverse drug reaction
AI	Active ingredient

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 23.3.2023 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.

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

- GC3110A is a quadrivalent influenza vaccine (split virion, inactivated), marketed as GCFLU quadrivalent in Korea since 2016.
- GC3110Ais a pre-filled syringe containing four (two type A and two type B) influenza virus strains recommended annually by the WHO. These viruses are individually cultivated in embryonated healthy flock eggs, inactivated and treated so that the integrity of the virus particles has been disrupted without diminishing the antigenic properties of the hemagglutinin and neuraminidase.
-It is indicated for active immunization of adults and children from 3 years 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.

3. Quality aspects:

1.2.1 Introduction

GC flu is a quadrivalent influenza vaccine (split virion, inactivated), indicated for active immunization of adults and children from 3 years 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.

1.2.2 Drug Substance (Active ingredient)

- **General information**

GC flu contains four (two type A and two type B) influenza virus strains recommended annually by the WHO. These viruses are individually cultivated in embryonated healthy flock eggs, inactivated and treated so that the integrity of the virus particles has been disrupted without diminishing the antigenic properties of the hemagglutinin and neuraminidase.

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

-DS is manufactured by GC Biopharma Corp. a biopharmaceutical company and its facilities are located in Hwasun-eup, Hwasun-gun, Jeollanam-do, Kore in accordance with good manufacturing practice.

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

-The manufacturing process for.

- All process steps and materials controls are well described.

- **Control of Materials**

Eggs:

- Healthy flock (non-SPF) eggs used in the manufacture of monovalent bulk (DS) are purchased from approved suppliers in Korea.
- All of the flock vaccination is confirmed by Certificate of Analysis (CoA) of approved suppliers. The suppliers also check the chicken flock to evaluate the infection of adventitious agents

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 and USP.

-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.

-viral seeds:

All Quality Control tests on the viral strains are performed by the respective World 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**

-In conclusion, the control system is considered adequate to monitor and control the active substance manufacturing process with regards to critical, non-critical operational parameters and in-process controls. Actions taken if limits are exceeded are specified. The methods used for the control of critical steps and intermediates have been described and validated.

- **Process Validation**

-Process validation and/or evaluation were conducted for the monovalent bulk (DS) of quadrivalent, inactivated influenza split vaccine.

-Following the annual WHO recommendation on the composition of seasonal influenza virus vaccine, critical manufacturing steps should be re-evaluated for the new strains.

-Process validations of critical steps are conducted for GC3110A to evaluate the process consistency for the new strains.
-several batches of GC3110A manufacturing process have been evaluated that results of all test items were met with the predefined acceptance criteria. According to the results, this process validation is provided the consistency and reproducibility of manufacturing process for GC3110A monovalent bulk (DS).

- **Manufacturing Process Development**

-Development of GC3110A was started to optimize the protection against circulating influenza B viruses. By adding a second type B virus of an alternate strain to the Korea licensed trivalent influenza vaccine (GC FLU pre-filled syringe Inj. approved in 2009) which is containing one H1N1strain, one H3N2 strain and one B lineages,
-GC3110A would provide broader protection against the influenza virus strains circulating during a particular epidemic season as quadrivalent vaccine.
-The two B strain in the GC3110A represent on strain of each of the two co-circulating influenza B lineages, B/Yamagata-like and B/Victoria-like which is recommend by WHO annually.
-Monovalent bulk manufacturing process of GC3110A and batch release acceptance criteria are identical to those for Korea approved GC FLU pre-filled syringe Inj..
Production conditions of monovalent bulk (DS) were already established through the development studies and process characterization.
-For the production of investigational product for phase 3 clinical trials, Green Cross Corporation developed a PFS scale up in 2014 – 2015 at GMP production site.
-Before commercial production, Drug product has been developed several scaled ups which were approved of Korea MFDS (Ministry of Food and Drug Safety) for commercial distribution in South Korea since 2016.
-As a result, it was confirmed that scaled-up development did not impact on robustness of manufacturing process and product quality.
-Detailed comparability studies for scaled up are provided.

- **Characterization**

- Full characterization has been performed on monovalent bulk (DS) with a variety of tests, including monovalent bulk (DS) release tests and the following additional characterization tests (Structural, physicochemical, immunological and biological characterizations).
-Product-related impurities are properly monitored during manufacturing, release and stability testing.
In addition, the process-related impurities were evaluated during commercial manufacturing

to demonstrate that the manufacturing process provides adequate removal of such impurities.

- **Specification**

-The release specification for the active substance comprises tests for identity, purity, potency and safety

-The specifications for the monovalent bulk of quadrivalent, inactivated influenza split vaccine (QIV) are established in accordance with the requirement of ICH Q6B.

-Most of specifications are satisfying the requirement of European Pharmacopoeia (Ph.Eur) unless otherwise specified.

- **Analytical Procedures**

- The analytical procedures (principle, equipment, standards/solution, procedure, measurement/ evaluation) are concisely described and the validation reports provided.

- All the non-compendial method were adequately described and appropriately validated in accordance to ICH guidelines.

- **Batch analysis**

-Commercial batches representing process validation analyses data were submitted and their results demonstrate that the monovalent bulk production process is consistent.

- **Reference Standards or Materials**

-The reference standard antigens and antisera are provided by NIBSC.

- **Container closure system**

- DS is stored in a single-use Flexboy® bag (EVA, ethylene vinyl acetate copolymer) manufactured by Sartorius.

-The specifications of Flexboy® bags from Sartorius and quality control test items for the components conducted at GC Biopharma Corp.are provided in the file.

-There are no increased impurities caused by extractable and leachable and there are no impacts of product safety.

- **Stability of drug substance**

-Based on available stability data

- ✓ **Approved shelf life for monovalent bulk:** 24 months
- ✓ **Approved shelf life for final bulk:** 12 months
- ✓ **Approved storage conditions for monovalent bulk and final bulk:** 2-8 °C

2.2.3 Drug product:

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

-The drug product is purified, inactivated monovalent bulk of four virus antigen type (A/H1N1, A/H3N2, B/Yamagata and B/Victoria).

-drug product is a single-use pre-filled syringe for injection, packaged in a 1 mL Type I clear glass syringe with needle, plunger rod and rubber stopper. Each syringe contains 0.5 mL of solution..

- **Pharmaceutical Development**

▪ **Components of drug product**

- The drug product contains four virus antigen (strain) monovalent bulk (A/H1N1, A/H3N2, B/Yamagata and B/Victoria) and it is formulated with phosphate buffer. Since circulating virus strains are different every year, virus antigens in GC3110A drug product are changed every year as recommended by WHO.

- Drug product is manufactured by blending four strain monovalent bulks (DS) with the phosphate buffer. The concentration of the drug product is 30 µg/mL of each strain.

▪ **Formulation Development**

-The GC3110A drug product formulation is 30 µg/mL of each four strain buffered with phosphate buffer containing sodium chloride, potassium chloride, disodium hydrogen phosphate dehydrate, and potassium dihydrogen phosphate.

-The phosphate buffer of GC3110A is commonly used in inactivated influenza vaccine.

▪ **Manufacturing Process Development**

-The manufacturing process of GC3110A drug product consists of blending, filling and packaging.

-These processes were developed as based on Korea licensed trivalent influenza vaccine. In manufacturing of GC3110A, there was addition of a second influenza type B virus compared with Korea licensed trivalent influenza vaccine in the formulation step, which is the development level of drug product.

▪ **Microbiological Attributes**

-GC3110A is a sterile solution for injection and aseptically filled drug product. The drug product formulation contains no antimicrobial preservatives.

-Sterility and endotoxin tests of the monovalent bulk (DS) and drug product are performed to ensure safety, and appropriate microbiological testing is performed during the manufacturing process and for the components of the drug product.

- **Compatibility**

-There are no reconstitution diluents or dosage devices associated with GC3110A drug product. The primary container closure system is the administration device for this product.
-Based on the stability results for DP contained in the primary container closure system, there is no abnormality observed in terms of interaction of DP with primary container closure system.

- **Manufacture of the drug product:**
  - **Description of manufacturing process and process controls along with manufacturers and responsibilities.**

Manufacturer:
-The finished product manufacturing and batch release take place at GC Biopharma Corp.
- The monovalent bulks are mixed and diluted and then, sterile filtration is performed to manufacture final bulk. After aseptic filling of container with final bulk, pre-filled syringes (PFS) are visually inspected. The qualified PFS is labeled and plunger rod assembled followed with blister packaging and carton packaging is conducted. After completion of carton packaging, the pre-filled syringes products (DP) are stored at 2 – 8°C.
- In conclusion, the applicant has provided a complete manufacturing process description including a general flow chart containing process parameters and in-process controls for each step. The critical steps, critical process parameters and in-process controls have been clearly identified.

- **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 batches of GC3110A manufacturing process have been evaluated that 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 for GC3110A drug product**.**

- **Product specification:**

-The specifications for drug product of quadrivalent, inactivated influenza split vaccine (QIV) is established in accordance with the requirement of ICH Q6B.
-Most of specifications are satisfying the requirement of European Pharmacopoeia (Ph.Eur) unless otherwise specified. The analytical methods have been developed and validated, when appropriate to support the current specifications.
-The specifications include appearance, general tests, test for identity, tests for purity, and tests for safety.
- Justification of the drug product specifications at the release and during stability studies are provided.
- All excipients used for GC FLU drug product are compendial, non-novel excipients such as (sodium chloride, potassium chloride,potassium dihydrogen phosphate) .
- No excipients of human or animal origin are used in the GC3110A drug product.
-no further impurities are introduced during the drug product manufacturing process

- **Reference Standards or Materials.**

A list of reference standards used by the applicant in the different release methods has been provided. No reference standard for the vaccine itself is expected, as the composition is subject to change every year according to the official recommendations.

- **Container closure system**
  - **Primary Packaging:**

-GC3110A final bulk is stored in a single-use Flexboy® bag (EVA, ethylene vinyl acetate copolymer) manufactured by Sartorius same as monovalent bulk solution (DS).
-The primary packaging used for finished product of GC3110A is composed of four components, Compatibility and stability of the drug product with the container closure system is provided.

- **Stability of the drug product**
  - ✓ **Approved shelf life for final bulk and finished product:** 12 months
  - ✓ **Approved storage conditions for finished product:** store at 2-8 ℃ without freezing in hermetic container and protect from light.

3. Non–clinical aspect:

- GC-FLU (GC3110A) is a purified IM Quadrivalent, inactivated vaccine indicated for prophylaxis against influenza caused by two type A and two type B strains of influenza virus in persons aged 6 months and older. This product was granted **WHO** prequalification on 12/04/2011 for the single (0.5 ml) and multiple (5 ml) dose vials.

- **Pharmacology:**

- In order to investigate the efficacy of GC3110A, an immunogenicity assessment was conducted in rats, rabbits and ferrets. In addition, protection efficacy was assessed in ferrets through A/H1N1 challenge test. The results showed that when GC3110A is intramuscularly injected at 2 or 3 weeks intervals, sufficient immunological reaction is induced in rats, rabbits and ferrets. In addition, protection against A/H1N1 virus is also confirmed in ferrets.

- As described in the Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines (CPMP/465/95), secondary pharmacodynamic, safety pharmacology & pharmacodynamic drug interaction studies were not conducted.

- **Pharmacokinetics:**

- As described in the Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines (CPMP/465/95), ADME (absorption, distribution, metabolism and excretion) was not conducted.

- **Toxicology:**

- Toxicological Studies were conducted in compliance with GLP guidelines as claimed by the applicant. **In the repeated dose toxicity study** performed on rabbits, no effect attributed to the administration of test article was observed in all male and female animals in terms of mortality & clinical signs. Test article-related histopathological changes observed in the spleen, popliteal lymph node, sciatic nerve and injection sites are expected for antigenic molecules. Based on these results, NOAEL for GC3110A was considered to be 1.0 mL/animal (2x the expected clinical dose). **In the reproductive/development toxicity study** performed in rats, any issue related to the administration of test article was not observed in either dams, embryo/fetus or offspring. L**ocl tolerance** was investigated in the repeat dose toxicity study; edema, and erythema/eschar formation were observed after administration of test article. However, the incidence and severity were low and improved over time.

- **Overall conclusion:** The efficacy and safety of GC3110A were demonstrated and no special concern regarding clinical application was raised. *Overall, the application **is approvable from the non-clinical point of view.***

4. Clinical aspect:

- **Clinical Pharmacology conclusion:**

The Regulation on Review and Approval of Biological Products allow exemption of ADME (absorption, distribution, metabolism and excretion) studies for vaccine products and so, the pharmacokinetics (PK) study is not required. Accordingly, the pharmacokinetics study was not conducted for GC3110A.

Information on pharmacodynamics (PD), such as seroconversion rate (SCR), seroprotection rate (SPR), geometric mean titers (GMT) and change ratio (before and after injection), obtained from clinical study of GC3110Ais provided in "results of Clinical Efficacy (Immunogenicity)".

- **Clinical Efficacy conclusion:**

After injection of investigational products into subjects of age 19 and older, HI antibody titers were measured and GMT and SCR results revealed that GC3110A is not inferior to GC FLUPrefilled Syringe Inj. and GC3110A (control drug).

When compared to GC FLUPrefilled Syringe Inj. and GC3110A (control drug) which contain one of two strain B antigens (Yamagata and Victoria), GC3110A containing both strain B antigens showed more effective immunological responses against such **additional strain B antigen** in terms of SCR, SPR, GMT and GMT ratio (before and after injection), in subjects aged >19 years.

Subjects aged ≥ 6 months to < 19 years showed immune reactions, where ‘GC3110A’met the FDA criteria by checking the seroconversion rate (SCR) and seroprotection rate (SPR) per 4 strains through HI antibody test.

Subjects aged ≥ 65 years also showed mmune reactions, where ‘GC3110A’satisfied the FDA criteria by checking the seroconversion rate (SCR) and seroprotectionrate (SPR) per 4 strains through HI antibody test.

In addition, subjects aged ≥ 6 months to <3 years showed that ‘GC3110A’ had immunogenicity satisfying the FDA criteria by checking the seroconversion rate (SCR) and seroprotection rate (SPR) per 4 strains through HI antibody test.

In conclusion, when compared to trivalent influenza split vaccine, which contains only one strain B antigens, the quadrivalent influenza vaccine, GC3110A, which contain both strain B antigens is considered to be more effective in prevention of influenza virus.

- **Clinical Safety conclusion:**

For the incidence rate of adverse events in test group (GC3110A), solicited local adverse events, solicited systemic adverse events and unsolicited adverse events were found in this **descending order** of incidence rates and most adverse events were "Grade 1" or "Grade 2".

The adverse events with high incidence rates in test group (GC3110A) were 'tenderness','pain''myalgia','fatigue',and'headache'in phase 1/2a and phase 3 clinical trials in adults. Similarly, in test group (GC3110A) in phase **3 clinical trial in children**, and in phase 3 clinical trial in the elderly, the incidence rate of 'tenderness', 'pain', 'fatigue(drowsiness)' and'malaise'was high,and in Part 2 in phase 3 clinical trial in infants, the incidence rate of 'pain/tenderness', 'drowsiness' and 'erythema/redness' was high. Most of the adverse events incurred were mild or moderate. In phase 3 clinical trial in adults, when compared to control group (GC FLUPrefilled Syringe Inj.) and GC3110A, test group (GC3110A) showed similar incidence rates of solicited systemic and unsolicited adverse events to control group.The incidence rates of serious adverse events incurred in phase 3 clinical trial in adults were **lower in test group** (GC3110A) (than control group GC F LU Prefilled Syringe Inj. (1.54 The incidence rates of serious adverse events incurred in phase 3 clinical trial in children were 0.9% and 1.0% in test group (G C3110A) and control group GC F LU Prefilled Syringe Inj. Inj.'', The incidence rates of serious adverse events incurred in test group (GC3110A) in phase 3 clinical trial in the elderly were **0.4%** and 1.1% in Step 1(Visit 1 Visit 3 and Step 2(Visit 1 Visit 4)), respectively The incidence rate of serious adverse events incurred in phase 3 clinical trial in infants was 8.1% and 7.7% in test group (and control group 'GC F LU Prefilled Syringe Inj.', respectively. All of serious adverse events incurred in clinical trials were not adverse drug reactions (ADR s When quadrivalent influenza vaccine GC3110A was compared with trivalent one, significant difference could not be found in terms of types and incidence rates of adverse events, incidence rates of serious adverse events, severity, trends in laboratory findings, vital signs and physical examinations.

5. Benefit/ Risk discussion: In conclusion the overall benefit/risk of product name is favorable in Prophylaxis against influenza caused by influenza A subtype viruses in persons aged 6 months and older.

6. General Conclusion and Recommendations if any:

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