Taiwan Food and Drug Administration

Assessment Report

Trade Name：福流佐四價流感疫苗 / FLUAD TETRA

Active Ingredient：

(1) **A/Victoria/2570/2019 IVR-215 (an A/Victoria/2570/2019 (H1N1) pdm09-like virus)**
(2) **A/Cambodia/e0826360/2020 IVR-224 (an A/Cambodia/e0826360/2020 (H3N2)-like virus)**
(3) **B/Victoria/705/2018 BVR-11 (a B/Washington/02/2019-like virus)**
(4) **B/Phuket/3073/2013 BVR-1B (a B/Phuket/3073/2013-like virus)**

License Number：MOHW-BI 001230

Applicant：台灣東洋藥品工業股份有限公司

Approval Date： 2023.03.03

Indication：
適用於 65 歲以上成人之主動免疫接種，預防此疫苗所涵蓋之兩種 A 型及兩種 B 型流感病毒所引起的流行性感冒。

FLUAD TETRA is indicated for active immunization of adults 65 years of age and older against influenza disease caused by influenza virus subtypes A and types B containing in the vaccine.

1. Background Information

Trade Name	福流佐四價流感疫苗 / FLUAD TETRA
Active Ingredient(s)	(1) A/Victoria/2570/2019 IVR-215 (an A/Victoria/2570/2019 (H1N1) pdm09-like virus) (2) A/Cambodia/e0826360/2020 IVR-224 (an A/Cambodia/e0826360/2020 (H3N2)-like virus) (3) B/Victoria/705/2018 BVR-11 (a B/Washington/02/2019-like virus) (4) B/Phuket/3073/2013 BVR-1B (a B/Phuket/3073/2013-like virus)
Applicant	台灣東洋藥品工業股份有限公司
Dosage Form & Strengths	注射劑
Indication	適用於 65 歲以上成人之主動免疫接種，預防此疫苗所涵蓋之兩種 A 型及兩種 B 型流感病毒所引起的流行性感冒。 FLUAD TETRA is indicated for active immunization of adults 65 years of age and older against influenza disease caused by influenza virus subtypes A and types B containing in the vaccine.
Posology	詳見仿單/ Please refer to the approved package insert
Pharmacological Category **ATC Code**	J07BB02

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The Drug Substance (DS) is composed of Haemagglutinin (HA) and Neuraminidase (NA) antigens from the four influenza virus strains recommended every year by the WHO for the Northern Hemisphere. The four strains used in the seasonal influenza vaccine consist of one influenza A (H1N1) virus, one influenza A (H3N2) virus, and two influenza B viruses.

The four DS (also referred as monovalent bulks) are produced and tested by Seqirus Vaccines Ltd (Liverpool, UK). The sufficient information of the manufacturing process for monovalent bulks have been provided. Briefly, each virus strain is inoculated into embryonated chicken eggs and the eggs are incubated at an optimum temperature for the virus propagation. After incubation, the virus containing allantoic fluid (AF) is harvested, centrifuged, filtered and concentrated. To achieve virus inactivation, a formaldehyde solution is added to concentrated AF under strain-specific conditions. Inactivated AF is further concentrated, purified and diafiltered. After diafiltration, the surface antigens are solubilized and split from the virus core. The resulting monovalent bulk is then sterile filtered into the containers. The manufacturing process controls are suitably defined.

The raw materials used for production of monovalent bulks are listed. The reference viruses were obtained from WHO collaborating centre. The chicken embryonated eggs used for the preparation of master and working seeds are specified pathogens free (SPF). The eggs used for production of monovalent bulks are derived from clinically healthy flocks. The preparation and release testing for master seeds and working seeds have been provided and considered appropriate. The provided information on the raw materials is considered adequate.

Process validation was successfully executed to assess each step of the monovalent bulk production process according to company procedures and parameters.

The specifications for all monovalent bulks are provided and considered acceptable. A description of each analytical procedure is provided. The method validation is sufficiently detailed. The DS batch analyses results comply with the specifications.

The reference materials including influenza reference antigens and influenza antiserum reagents are sourced from WHO Collaborating Centre. The antigen/antiserum reagents are qualified, and the reagent qualification reports are provided.

A shelf life of 12 months for each monovalent bulk is supported by the data provided.

2.1.2 Drug product

The finished product is a combination of four DS, MF59C.1 adjuvant and buffer solutions. The vaccine is supplied as a 0.5 mL single dose sterile suspension for injection in a milky-white emulsion, contained in a Type I glass pre-filled syringe with an affixed needle.

Adjuvanted Quadrivalent Influenza Vaccine (aQIV) is manufactured as an aseptic formulation in a closed system. Formulation involves the addition of the required four DS, phosphate buffered saline (PBS), water for injection (WFI), a stabilising solution and MF59C.1 adjuvant to a formulation vessel. The components are mixed and sampled for testing. The influenza monovalent bulks, PBS buffer and MF59C.1 adjuvant produced from the stored bulk adjuvant are sterile filtered prior to formulation.
Aseptic filling of aQIV is performed in zone A isolator. The necessary in process controls have been identified for each stage of the manufacturing process.

aQIV formulation and filling operations conducted in Seqirus Vaccines Ltd (Liverpool, UK) have been fully validated and details are provided.

The excipients used for the aQIV formulation include: sodium chloride, potassium chloride, potassium dihydrogen phosphate, disodium phosphate dihydrate, magnesium chloride hexahydrate, calcium chloride dihydrate, MF59C.1 and water for injections. All components comply with the current edition of the USP and Ph. Eur. monographs.
MF59C.1 adjuvant is an oil-in-water emulsion. The manufacturing process of MF59C.1 has been provided. The appropriate process controls (including critical process parameters and in-process controls) are defined for its manufacture. The MF59C.1 bulk adjuvant process validation has been successfully completed.

The specifications proposed for release of the final quadrivalent bulk, final filled vaccine and packed product have been provided. The specifications are acceptable.
The non-compendial analytical procedures used for release testing have been successfully validated. The compendial methods used have been appropriately validated/verified.

An appropriate number of process performance qualification batches of aQIV were formulated and filled into pre-filled syringes at the Seqirus Vaccines Ltd (Liverpool, UK) site. All the results for the PPQ batches met the acceptance criteria.

aQIV is supplied to the market in a pack of 10 of single 0.5 mL pre-filled syringes with an affixed needle. The sufficient information of individual components and materials for container closure system is provided.

A 12-month shelf life for the final product (PFS) at 2-8°C, protected from light, is supported by the provided data.

2.2 Preclinical Pharmacology/Toxicology Evaluation

The nonclinical data supporting aQIV is based on studies performed with aQIV, Fluad® (aTIV), or formulations that are equivalent to Fluad (TIV+MF59) or aQIV (Fluad High B).

In mice, even in seropositive mice, immunization with TIV or in combination with MF59 (aTIV) via SC or IM routes elicited a dose-related antigen-specific antibody response. Immunization also induced the lymphoproliferative response of splenocytes in an in vitro assay.

In aTIV-immunized mice challenged with lethal doses of seasonal influenza virus, dose-dependent reduction in lung viral load and increased survival were shown. The protection against challenge lasted for up to 200 days post-immunization. The inclusion of MF59 in aTIV increased the antibody response in both young and old mice and provided full protection for mice against a lethal viral challenge with fewer antigens required.

The toxicology program consists of GLP studies in Guinea pigs and rabbits. In the pivotal GLP study in rabbits, Q2W, IM administration of 3 full human doses of a formulation equivalent to aQIV was immunogenic and well tolerated. No local or systemic adverse effects were notable. The 3-dose regimen administered 14 days apart in the GLP pivotal study exceeds the number of doses proposed in humans, and the dose in rabbits equals the clinical human dose in terms of absolute dose.

The rabbit pivotal GLP study identified no harmful effects of the vaccine on the reproductive organs. In a GLP reproductive and developmental toxicity study in rabbits, IM administration of a full human dose of aTIV (45 mcg HA) twice before mating and twice during gestation was well-tolerated and immunogenic in maternal rabbits, and the antibodies were present in the fetuses and persisted to 4 weeks post-natal in the offsprings. No effects on female fertility, maternal or embryofetal toxicity, teratogenicity, and effects on post-natal development were observed.

Local tolerance evaluated in the pivotal GLP repeated-dose study in rabbits only showed partially to fully recoverable findings with low grades of severity. In general, the vaccines were well-tolerated locally. In Guinea pigs, TIV adjuvanted with MF59C.1 did not cause delayed contact hypersensitivity.

In accordance with guidelines on the nonclinical development of vaccines, no secondary pharmacodynamics studies and dedicated safety pharmacology studies performed with aTIV or aQIV is considered acceptable. So far, experiences with MF59-adjuvanted influenza vaccines do not indicate effects other than those of the immune system. Also, it is acceptable that no genotoxicity and carcinogenicity studies have been performed with aQIV or aTIV formulations.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The sponsor provides a pivotal study [V118_18] and an immunogenicity study [V118_20] to support the efficacy of Fluad Tetra for the claimed indication.

Study [V118_18]

Study V118_18 was a Phase 3, randomized, observer-blind, controlled study to compare Fluad Tetra with Boostrix (Tdap) in adults ≥ 65 years of age. For vaccine efficacy, the primary endpoint was time to first-occurrence of RT-PCR-confirmed influenza due to any strain from 21 through 180 days after vaccination or end of the influenza season, whichever was longer. There were 122 cases in the Fluad Tetra group, and 151 in the Boostrix group. Most of the cases were A/H3N2 antigenically unmatched to the vaccine strain. The vaccine efficacy was 19.80% and the lower limit of the 97.45% CI was -5.27%. The primary endpoint did not meet success criteria (lower limit > 40%).

For immunogenicity, the lower limit of the 95% CI for the percentages of subjects with a HI titer ≥ 1:40 was 95.05% in A/H1N1, 94.37% in A/H3N2, 76.95% in B/Yamagata and 79.39% in B/Victoria. The lower limit of the 95% CI for the percentages of subjects who achieved seroconversion was 75.66% in A/H1N1, 82.52% in A/H3N2, 58.06% in B/Yamagata and 62.88% in B/Victoria. All four strains met CBER criteria (seroprotection [HI titer ≥ 1:40] rate: lower limit ≥ 60%；seroconversion rate: lower limit ≥ 30%).

Study [V118_20]

Study V118_20 was a Phase 3, randomized, double-blind, controlled study to compare Fluad Tetra (aQIV) versus the licensed Fluad (aTIV-1) and aTIV-2 that contained the alternate B strain in adults ≥ 65 years of age. For co-primary endpoint 1 (noninferiority of aQIV vs. aTIV-1 and aTIV-2), the upper bound of the two-sided 95% CI for the GMT ratios was 1.27 in A/H1N1, 1.09 in A/H3N2, 1.08 in B/Yamagata and 1.08 in B/Victoria, which were all smaller than 1.5. The upper bound of the two-sided 95% CI for the seroconversion rate difference was 7.76% in A/H1N1, 4.96% in A/H3N2, 3.27% in B/Yamagata and 2.55% in B/Victoria, which were all smaller than 10%. The co-primary endpoint 1 noninferiority

criteria was met for all 4 strains.

For co-primary endpoint 2 (CBER Immunogenicity Criteria), the lower limit of the 95% CI for the percentages of subjects who achieved seroconversion was 32.03% in A/H1N1, 36.08% in A/H3N2, 14.00% in B/Yamagata and 11.22% in B/Victoria. The lower limit of the 95% CI for the percentages of subjects with a HI titer ≥ 1:40 was 66.20% in A/H1N1, 92.12% in A/H3N2, 29.69% in B/Yamagata and 34.95% in B/Victoria. A strains met both of the CBER criteria, but B strains did not. Similar trend was observed for licensed aTIV. The reasons for systemic shift (decrease) of HI titers in this study was justified.

2.4.2 Safety Results

The observed rates of solicited local AEs were slightly higher in the aQIV group compared with aTIV groups. The incidence rates of solicited systemic AEs and unsolicited AEs were similar across groups. The most common solicited local AE was injection site pain. The most common solicited systemic AEs were headache and fatigue. Overall, the safety profile was similar between aQIV and aTIV.

2.5 Bridging Study Evaluation

In Study V118_18, 2287 subjects were enrolled from Asia, and 4453 subjects were enrolled from non-Asia. In general, vaccine efficacy and safety profile were similar between Asian and Non-Asian population. The Day 22/Day 1 GMT ratio and seroconversion rate of A/H3N2 strain was lower in the Asian population compared with non-Asian population, which may be contributed to higher baseline GMT. The percentage of subjects who had HI titer ≥ 1:40 at Day 22 was similar between Asian and non-Asian population. All four strains met the CBER criteria in Asian population. In conclusion, the ethnic difference was minimal and bridging study could be waived.

2.6 Conclusion

Fluad Tetra as the active immunization against influenza disease caused by influenza virus subtypes A and types B containing in the vaccine in adults 65 years of age and older demonstrates a favorable risk-benefit profile to recommend regular approval.

3. Post-Marketing Requirements

The ongoing confirmatory efficacy trial V118_24 requested by USFDA should be submitted for review once completed.