PUBLIC ASSESSMENT REPORT
FOR
Fluarix-Tetra

Common Name: Quadrivalent influenza vaccine (split virion, inactivated)

vaccine

Application No. 2 C 90004/56 (NB)

Assessment Report as adopted by the TFDA with
all information of a commercially confidential nature deleted

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant GlaxoSmithKline (Thailand) Ltd. submitted on 9 April 2013 an application for Marketing Authorization to the Thailand Food and Drug Administration (TFDA). At the time of submission and validation, Fluarix™ Tetra was designated as medicinal product in the following indication: For active immunisation of adults and children from 3 years of age for the prevention of influenza disease caused by influenza virus types A and B contained in the vaccine.

The legal basis for this application refers to: Drug Act 2510 B.E.

The application submitted was a complete dossier: composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature substituting/supporting certain tests or studies.

Licensing status:

The product was licensed in European countries at the time of submission of the application.

TFDA Product Team Leader: (PTL)

Mr. Pramote Akarapanon

TFDA External Experts

- Quality:
    1. ผู้อำนวยการสถาบันชีววัตถุ
    2. ผศ.ดร.วิสิฐ ตั้งเคียงศิริสิน

- Non Clinical
    1. รศ.ดร.โสภิต ธรรมอารี
    2. รศ.ดร.นงลักษณ์ สุขวาณิชย์ศิลป์

- **Clinical**
    1. ศ.นพ.ประเสริฐ ทองเจริญ
    2. รศ(พิเศษ) ทวี โชติพิทยสุนนท์

1.2 Steps taken for the assessment of the product

- The application was received by the TFDA on 9 April 2013.
- The procedure started on 23 August 2013.
- A List of questions, the overall conclusion and review of the scientific data were prepared by the TFDA's PTL and sent to the applicant
- The applicant submitted of the responses, including revised SPC, labeling and package leaflet texts in English and/ or Thai (where required by Drug Act)
- TFDA prepared preliminary Assessment Report based on responses from the applicant and dispatched the assessment report to external experts for their consideration and comments
- During the In dept assessment the external experts agreed on the consolidated List of Questions to be sent to the applicant.

- TFDA considered the consolidated list of questions, identifying "major objections" and/or "other concerns" may be adopted. These were sent to the applicant together with the TFDA recommendation and scientific discussion
- Final draft of English SPC, labeling and package leaflet was sent by applicant to the TFDA PTL
- TFDA adopted the decision on marketing authorization

2. SCIENTIFIC DISCUSSION

2.1 Introduction

2.2 Quality aspects

Introduction

Fluarix Tetra is a quadrivalent influenza-virus vaccine, presented as suspension for injection in prefilled syringe. It contains antigens from two influenza A subtype viruses (subtypes H1N1 and H3N2) and two type B viruses (Victoria and Yamagata strains) which virus strains have been based on the WHO yearly recommended composition.

Fluarix Tetra is a preservative-free (thimerosal-free) vaccine which no thimerosal in any composition and each steps of production. The formulation utilises the same starting materials and manufacturing and control processes, equipment and facilities, as currently licensed for the Fluarix trivalent vaccine.

Each dose (0.5 ml) contains.

Active Substances:

Purified antigen fractions of

Monovalent inactivated split-virion: A/H1N1	15 µg haemagglutinin
Monovalent inactivated split-virion: A/H3N2	15 µg haemagglutinin
Monovalent inactivated split-virion: B strain (Victoria lineage)	15 µg haemagglutinin
Monovalent inactivated split-virion: B strain (Yamagata lineage)	15 µg haemagglutinin

Excipients:

Polysorbate 80 (Tween 80)

α-tocopheryl hydrogen succinate

Octoxinol 10 (Triton® X-100)

Sodium chloride

Magnesium chloride hexahydrate

Disodium phosphate dodecahydrate

Potassium dihydrogen phosphate

Potassium chloride

Water for injections

Manufacturers

Manufacturing Facility	Operations
GlaxoSmithKline Biologicals Branch of SmithKline Beecham Pharma GmbH & Co.KG Zirkusstrasse 40 D-01069 Dresden Germany	Formulation of drug product
GlaxoSmithKline Biologicals Branch of SmithKline Beecham Pharma GmbH & Co.KG Zirkusstrasse 40 D-01069 Dresden Germany And/Or : GlaxoSmithKline Biologicals Parc de la Noire Epine, Rue de Fleming 20, 1300 Wavre, Belgium	Filling and inspection of drug product

GlaxoSmithKline Biologicals Branch of SmithKline Beecham Pharma GmbH & Co.KG Zirkusstrasse 40 D-01069 Dresden Germany And/Or : GlaxoSmithKline Biologicals Parc de la Noire Epine, Rue de Fleming 20, 1300 Wavre, Belgium And/Or : GlaxoSmithKline Biologicals Rue des Aulnois 637 F-59230 Saint-Amand-les-Eaux, France	Labeling and Packaging of drug product
GlaxoSmithKline Biologicals Branch of SmithKline Beecham Pharma GmbH & Co.KG Zirkusstrasse 40 D-01069 Dresden Germany And/Or : GlaxoSmithKline Biologicals Parc de la Noire Epine, Rue de Fleming 20, 1300 Wavre, Belgium	QC testing of drug product
GlaxoSmithKline Biologicals Branch of SmithKline Beecham Pharma GmbH & Co.KG Zirkusstrasse 40 D-01069 Dresden Germany	Batch release of drug product

I. DRUG SUBSTANCE(S)

3. General Information, Starting Materials and Raw Materials

The drug substance is composed of inactivated split-virus antigen of each of the four strains recommended by the WHO for inclusion in the quadrivalent influenza vaccine. Two of these strains are from A subtypes and two of B subtypes. The second B strain belongs to the

opposite lineage (Yamagata/Victoria) as the strain currently recommended for trivalent composition.

4. Manufacturing Process of the Drug Substance(s)

A Master and a working seed were prepared for each of the virus strains, received from the WHO Reference centre. The manufacturing process for the monovalent bulk is identical to the manufacturing process for the monovalent bulks of the licensed product Fluarix and can be divided into four main parts:

-Propagation of the working seed in fertilized hen's eggs, harvesting and pooling of infected allantoic fluids

-Splitting of the monovalent with sodium deoxycholate

-Purification of the whole virus

-Inactivation of the purified monovalent split virus using sodium deoxycholate

The process is derived from Fluarix process and is the same.

3 Characterization of the Drug Substance(s)

The active pharmaceutical ingredients (API) in influenza subunit vaccines are viral haemagglutinin (HA) and neuraminidase (NA) proteins. Appropriate activity and quantity of these proteins are generally conducted with international reference standards intended for conventional, egg-derived antigens.

4 Quality Control of the Drug Substance(s)

The specifications for the drug are in-line with the European Pharmacopeia (EP) monograph for Influenza Vaccine (split virion inactivated). The specification for residual sodium deoxycholate for the H1 and B strain was increased from ≤100 to ≤160 µg/mL due to the change in dilution factors required for the QIV.

Appropriate validation data have been submitted in support of the test procedures.

5 Reference Standards or Materials

The descriptions of the reference materials are satisfactory.

6 Packaging and Container Closure System of the Drug Substance(s)

The monovalent bulks are stored in 10 L Duran® glass bottles closed with polypropylene caps or in 50 L plastic bags (Flexboy® bags) closed with a pinch clamp at the bag tubing. According to the applicant, all primary container system comply with the requirements European pharmacopoeia guidelines. Specifications have been provided for the Flexboy® bags. For the glass bottles quality control is performed by the vendor (Duran Schott).

7 Stability of the Drug Substance(s)

Real-time stability studies for the four monovalent bulks covering 12 months at +2°C to +8°C for both container systems have been supported non significant change in HA content, sterility and endotoxin including ∝-TCS.

II. DRUG PRODUCT

1 Description and composition of the Drug Product

Fluarix Tetra is a quadrivalent inactivated, split virion seasonal influenza vaccine. It contains four influenza strains, two A (A/H1N1 and A/H3N2) and two B (one each of the Victoria and Yamagata lineages) strains, following evaluations and recommendations by the World Health Organization (WHO). The vaccine is formulated with a diluent to contain a minimum of 15 µg of Ha per strain, 60 µg per dose.

2 Pharmaceutical Development

The Fluarix Tetra drug product development is based on GSKs licensed seasonal trivalent influenza vaccine Fluarix, taking into consideration the addition of a fourth active substance. It is formulated to a minimum HA concentration of 15 µg HA per strain per 0.5 mL dose. In addition, an HA overage is applied for each strain to ensure potency of the vaccine throughout its shelf-life, and to compensate for possible inter-laboratory variability of the HA content test method. The same excipients are found in both vaccines. There is no excipient of human or animal origin, or novel excipient in the vaccine. Polysorbate 80 (Tween®-80) and octoxinol 10 (Triton® X-100) are detergents used to solubilize the HA antigens. ∝-Tocopheryl hydrogen succinate is used to stabilize the HA antigens. The targeted detergent/stabilizer to-HA ratios are the same between Fluarix and Fluarix Tetra.

3 Manufacturing Process of the Drug Product

The manufacturing process for the Fluarix Tetra drug product has been developed based on the Fluarix drug product manufacturing process and consists of the following steps:

- Formulation of the final bulk;
- Transfer of the final bulk into GSK network for filling (when filling takes place outside the formulation site);
- Filling (including stoppering) and inspections of the final containers;
- Transfer of the final containers into GSK network for labeling and packaging (when labeling and packaging take place outside the filling site);
- Labeling and packaging of the Fluarix Tetra final product.

The process uses the same starting materials, equipment and facilities as Fluarix. The development of the manufacturing process is limited to the production scale-up and to technical adjustments during the formulation process.

4 Control of the Adjuvant(s), Preservative(s), Stabilizer(s), and Excipients(s)

Specifications for excipients and analytical procedures are in line with the Ph.Eur.

5 Quality Control of the Drug Product

The specifications for the Fluarix Tetra final bulk product and the final container product are considered acceptable and justified as they are the same as the trivalent vaccine. The final bulks tests are protein content, alpha-TCS content, octoxinol 10 content, polysorbate 80 content, pH, formaldehyde content, ovalbumin content, sterility, potency influenza haemagglutinin. Tests in the final container are description, iendity, sterility, pH, voume, potency and endotoxin content. The manufacturer has exemption on the Abnomral toxicity test (ATT) in final container with the reference to the historical data of Fluarix™ which is acceptable.

The in-house developed validation of analytical methods are protein content, alpha-TCS content, octoxinol 10 content, polysorbate 80 content, formaldehyde content, ovalbumin content, potency and identity. The results are in the acceptance limit. Batch analysis results shows consistency and met the proposed specifications.

6 Reference Standards and Materials

Reference standard used for the single radial diffusion (SRD) assay for potency and identity compose with reference antigens and antiserum from WHO Reference Laboratories.

7 Packaging and Container Closure System of the Drug Product

Fluarix-Tetra is in the pre-filled syringe which is compatible with the vaccine.

8 Stability of the Drug Product

These stability results comply with the specifications and are stable, up to 15 months storage at 2 to 8°C. The proposed 12 month shelf life storage at 2-8 °C was acceptable.

III. APPENDICES

The following information may be needed on a case by case basis.

1 Equipment and Facilities

N/A

2 Evaluation of the Safety of Adventitious Agents

N/A

The TFDA recommended on The Quality Dossiers as The followings: N/A

The company responded to the above recommendations as the followings: N/A

TFDA PTL AND EXTERNAL EXPERT'S OVERALL CONCLUSIONS ON QUALITY ASPECTS

The chemical, pharmaceutical and biological documentation in support of this application have been evaluated. The overall Quality of Fluarix Tetra is considered acceptable.

BASED ON THE RESULTS THESE QUALITY ASPECT COULD BE ACCEPTED

2.3 NonClinical aspects

Introduction

Antigens contains in Fluarix Tetra is the same as in Fluarix while other new developed influenza vaccines by GSK contains ASO3 adjuvant such as Flu NG and Flu NG QIV. Non-clinical data including safety and immunogenicity profiles of Fluarix Tetra is mostly from data FluNG and Flu NG QIV vaccine.

I.PHARMACOLOGY

Pharmacology data generated early in mice revealed that non-adjuvanted Flu-D-QIV is poorly immunogenic compared with adjuvanted formulations. In contrast, in clinical setting the non-adjuvanted Flu-D-QIV could induce satisfactory antibody responses to each vaccine antigens in

adults and children and the addition of the second B strain does not cause antigenic interference. This discrepancy may be due to inter-species difference in immune system.

The Applicant assumed that there were no suitable animal models to test immunogenicity/efficacy of non-adjuvanted influenza vaccines. However, review of the toxicological testing programme revealed that non-adjuvanted influenza vaccines Fluarix and Flu-D-QIV can be immunogenic in rabbit and rat species.

Nonetheless, no additional immunogenicity studies in animal models are deemed necessary for this initial MAA.

1 Pharmacodynamic studies (immunogenicity of the vaccine)

-

2 Pharmacodynamic studies of adjuvant(s) (if applicable)

-

II.PHARMACOKINETICS

No Pharmacokinetic study of Fluarix Tetra, This is aligned with international guidelines such as the CPMP/SWP/465/95.

III. TOXICOLOGY

1. General toxicology

The single dose toxicity, repeated dose toxicity and local tolerance studies conducted in New Zealand white rabbit using AS03-adjuvanted Trivalent and Quadrivalent seasonal influenza vaccines (FluNG TIV and QIV) as well as the non-adjuvanted Trivalent seasonal influenza vaccine. In these studies, full human doses (corresponding to 60 µg HA in Quadrivalent and 45 µg HA in Trivalent test vaccines) under the intramuscular route of administration have been tested. No safety concerns were raised. The results cross these studies were consistent and typical for a vaccine product, like a transient local inflammation at injection site primarily with adjuvanted formulations, and some reversible changes in clinical pathology parameters. Relevance of this rabbit species and animal exposure to the test vaccines were supported by serological data collected from repeated dose toxicity studies.

2. Special toxicology for vaccines (when applicable)

2.1 Special immunological investigations

- **Toxicity studies in special population**
- **Genotoxicity and carcinogenicity studies, when applicable**
- **Reproductive toxicity studies for vaccines to be administered to pregnant women or individuals of fertile age.**

Two reproductive and developmental toxicity studies were performed in rats, using non-adjuvanted formulations of Dresden and Quebec seasonal Trivalent and Quadrivalent influenza vaccines. The dose levels (total HA contents per dose) administered intramuscularly were 24 µg HA/dose for Quadrivalent and 9 µg HA/dose for Trivalent test vaccines, which correspond to greater than 80-fold and 30-fold the human doses on a body weight basis, respectively. There were no test vaccine-related treatment effects on embryo-fetal and peri- and post-natal development. No sign of maternal toxicity including mating performance, fertility, or ability to produce a live litter, were observed. Relevance of this rat species and animal exposure to the test vaccines were supported by serological data collected from these two studies. However, relatively low GMC was noted in GD 20 fetuses of the D-QIV group (1.904 µg IgG/mL). Preliminary studies performed for immunogenicity of all vaccine antigens in rat species revealed that B/Brisbane/60/2008 (Victoria) selected was the most immunogenic in rat species.

3. SPECIAL CONSIDERATIONS (if applicable)

3.1 Live attenuated vaccines.

N/A

3.2 New substances incorporated into the formulation

4. TFDA PTL AND EXTERNAL EXPERT'S COMMENTS ON THE SPC, LABELS AND PACKAGE LEAFLET

There are no non-clinical outstanding concerns to object to the approval of Fluarix Tetra.

5. TFDA PTL AND EXTERNAL EXPERT'S OVERALL CONCLUSIONS ON NON-CLINICAL ASPECTS

There are no nonclinical objections to registration, provided that the clinical data demonstrate satisfactory vaccine efficacy/immunogenicity.

BASED ON THE STUDIES DESIGN AND RESULTS THESE NON-CLINICAL ASPECT COULD BE ACCEPTED

2.4 Clinical aspects

Introduction

The applicant has developed a quadrivalent influenza virus vaccine : the quadrivalent candidtate vaccine (D-QIV), is a split-virion, inactivated influenza vaccine that contains three strains annually recommended by WHO (two A-strains and one B-strain) and second B strain, belowning to the opposite lineage as the B strain currently recommended for trivalent vaccine (TIV) composition, and that is shown to co-circulate in the human population.

The vaccine is proposed for the active immunization for adults and children from 3 years of age against influenza disease caused by influenza virus types A and b contained in the vaccine. The D-QIV induces humoral antibodies against hemagglutinins. These antibodies neutralize influenza viruses.

1. REPORTS OF CLINICAL STUDIES

1 Phase I Studies

Phase I/II study has been evaluated with other Phase III studies.

2 Phase II Studies

Phase II studies has been evaluated with other Phase III studies.

3 Phase III Studies

The dossier included 6 clinical studies to demonstrate efficacy and safety of Fluarix Tetra as following.

1. 2 Pivotal clinical studies
   - 1.1 Study D-QIV-008 (phase III study) evaluated the candidate D-QIV vaccine in adults from 18 years of age, total 2,951 subjects.
   - 1.2 Study D-QIV 003 (phase III study) evaluated the candidate D-QIV vaccine in subject age from 6 month old to 17 years, total 2,645 subjects However, company has brought the data from subject aged 3-17 years to evaluate the clinical study.
2. 2 Supportive clinical studies

2.1 Study D-QIV-001 (phase I/II study) evaluated the candidate D-QIV vaccine in adults from 18-60 years of age, total 417 subjects.

2.2 Study D-QIV-002 (phase II study) evaluated the candidate D-QIV vaccine in adults from 18-47 month old, total 585 subjects.

3. Clinical study of Fluarix™ to evaluate GSK Biologicals' trivalent vaccine in 6 to 35 month old. The studies is to support immunogenicity and pediatric dose-selection of Fluarix Tetra

3.1 Study Fluarix-US-006 (phase IV study) evaluated the Fluarix vs placebo as control in adults from 18-64 years of age, total 7,652 subjects.

3.2 Study Fluarix-US-007 (phase III study) evaluated Fluarix in children 6-35 month old, total 3,317 subjects

Study Fluarix-US-006 (phase IV) evaluated the efficacy, safety and immunogenicity of Fluarix™ versus placebo. Results from this study revealed 66.9% of Fluarix™ protective efficacy which will be used as supportive efficacy data, as well as a basis for the non-inferiority approach taken in the clinical development of the D-QIV candidate vaccine.

Study Fluarix-US-007 (phase III) evaluated Fluarix in children 6-35 month old. This study supporting the paediatric dose selection in children below 3 years of age for the D-QIV candidate vaccine. However, company did not propose the data from this study hence the proposed indication is for children from 3 years onward.

Four studies, D-QIV-008, D-QIV-003, D-QIV-001 and D-QIV-002, evaluated immunogenicity, non-inferiority and superiority of the antibody response against the 4th, additional B strain (i.e. not included in TIV but included in D-QIV), following D-QIV vaccination compared to TIV and also demonstrated reactogenicity and safety. Results from the four studies support the non-inferiority of the Haemagglutination Inhibition (HI) antibody response against the TIV in both adults and children 3 years of age and older and superiority of the HI antibody response against the additional lineage B strain as well as the clinical lot-to-lot consistency of the HI immune response-evaluated in adults from study D-QIV-008.

4 Special Considerations

Data contained in Fluarix Tetra registration document seems acceptable. No special consideration.

5 Adjuvant(s)

No information on the adjuvant as no adjuvant as a component for Fluarix Tetra.

6 Phase IV Studies and / or Pharmacovigilance plan (if applicable)

No phase IV clinical study for Fluarix Tetra, the company has phase IV clinical study of Fluarix - Study Fluarix-US-006. As the results have been used to support Fluarix Tetra efficacy as well as the non-inferiority for Fluarix Tetra which is acceptable.

7 Non-inferiority Studies (for combined vaccines, or approved vaccines prepared by new manufacturers)

The applicant has conducted the non-inferiority of Fluarix Tetra when compared to Fluarix as mentioned in Phase III studies. It demonstrated immunogenicity in adult and children 3 years of age and older, following vaccination with Fluarix Tetra when compared to Fluarix and superiority of the antibody response against the additional lineage B strain.

8 Co-administration Studies with other Vaccines

Currently, no co-administration study with other vaccine. Company has conducted the co-administration study of Fluarix Tetra and Pneumovax 23 (study D-QIV-010) in subjects at risk aged 50 years and older to evaluate the immunogenicity, reactogenicity and safety. After the study completed, the prescribing information should be revised in accordance to the results of this study.

2. TFDA PTL AND EXTERNAL EXPERT'S COMMENTS ON THE SPC, LABELS AND PACKAGE LEAFLET

Results from clinical studies justified the content in the prescribing information.

3. TFDA PTL AND EXTERNAL EXPERT'S OVERALL CONCLUSION ON CLINICAL ASPECTS

From the overall From the overall study results it can be concluded that Fluarix Tetra will be at least as efficient as the trivalent comparator Fluarix as evidenced from efficacy data generated with the latter vaccine and immunogenicity data extrapolated from this specific efficacy study to all immunogenicity study conducted with D-QIV. Moreover, given superior immunogenicity of Fluarix Tetra and the presence of the second B strain it can be expected that overall vaccine efficacy in this age group is higher compared to trivalent influenza vaccines. The reactogenicity and safety profile safety of Fluarix Tetra appears to be similar to Fluarix.

BASED ON THE STUDIES DESIGN AND RESULTS THESE CLINICAL ASPECT COULD BE ACCEPTED

2.5 Pharmacovigilance (If applicable)

N/A.

2.6 Overall Conclusion on Risk/benefit Assessment and Recommendation

Efficacy

The immunogenicity of Fluarix Tetra has been demonstrated in adults and children from 3 years of age.

Safety

The safety of Fluarix Tetra studied in the aged groups proposed for registration apprears to be similar to that of the registered trivalent vaccines.

Benefits

Clinical efficacy of Fluarix Tetra has not been determined. But the risk benefit balance was considered to be on the side of benefit. Registration of Fluarix Tetra was recommended.

Recommendations

The TFDA and external experts have reviewed the clinical studies and found them evidently supportive; therefore positive opinion was given towards the approval of marketing authorization of Fluarix Tetra with conditions requesting the applicant to follow the SMP protocol.