Summary Basis for Regulatory Action

Date: November 18, 2016

From: Helen S. Gemignani, Chair of the Review Committee

BLA/ STN#: 125127/775

Applicant Name: GlaxoSmithKline Biologicals

Date of Submission: January 20, 2016

Goal Date: November 20, 2016

Proprietary Name/Established Name: Fluarix® and Fluarix® Quadrivalent, Influenza Vaccines

Indication: Active immunization in persons aged 3 years and older for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine.

Recommended Action: The Review Committee recommends approval

Review Office Signatory Authority: Wellington Sun, MD, Director, Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review

□ **I concur with the summary review.**

□ **I concur with the summary review and include a separate review to add further analysis.**

□ **I do not concur with the summary review and include a separate review.**

Document title	**Reviewer name, Document date**
Clinical Reviews • *Clinical (OVRR/DVRPA)* • *Bioresearch Monitoring(OCBQ/DIS)*	 Sarah Browne, MD, 11/16/16 Dennis Cato, 8/11/16
Statistical Reviews • *Clinical data (OBE/DB)* • *Non-clinical data (OBE/DB)*	 Yin Kiu Cheung, PhD, 10/06/16 Yin Kiu Cheung, PhD, 10/05/16

Document title	Reviewer name, Document date
CMC Reviews • *CMC (OVRR/DVP)* • *Facilities review (OCBQ/DMPQ)* • *Product Quality and Testing* (OCBQ/DBSQC) • *Product Quality and Testing* (OCBQ/DBSQC) • *Product Quality and Testing* (OCBQ/DBSQC)	Olga Zoueva, PhD, 11/04/16 Ellen Huang, 3/30/16 and 11/04/16 Manju Joshi, PhD, 10/28/16 Hyesuk Kong, PhD, 10/20/16 Kouassi Ayikoe, PhD, 9/15/16
Toxicology Review • *Toxicology (OVRR/DVRPA)*	Ching-Long Sun, PhD, 10/20/16
Labeling Review • Labeling (OVRR/DVRPA)	Stephanie Polo, 11/14/16
Advisory Committee Transcript	N/A

1. Introduction

This Prior Approval Supplement was submitted by GlaxoSmithKline (GSK) to the Center for Biologics Evaluation and Research (CBER) to support Drug Substance manufacturing changes for the licensed seasonal influenza vaccines, Fluarix® and Fluarix® Quadrivalent. The requested changes are intended to harmonize and streamline production, reduce overall process complexity, simplify procedures, and eliminate strain-specific media and components in the monovalent bulk manufacturing process for both seasonal vaccines. The drug product manufacturing process is not affected by these changes and there is no change in approved release specifications for Drug Substance or Drug Product.

2. Background

Fluarix vaccines are indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine and is approved for use in persons aged 3 years and older and administered as a single 0.5 ml dose. Children aged 3 to less than 9 years who have not previously been vaccinated against influenza should receive a second dose of 0.5 ml after an interval of at least 4 weeks. The trivalent formulation of Fluarix contains 15µg each of three detergent-split antigens: two A-type strains and one B-type strain; the quadrivalent formulation contains the same three strains as that of the trivalent formulation plus an additional influenza B strain.

Fluarix was approved on August 31, 2005, under accelerated approval regulations for active immunization of adults aged 18 years and older against influenza disease. After submission of data from confirmatory clinical studies to verify and describe clinical benefit, Fluarix was granted 'traditional approval' on October 2, 2009. Expansion of the age indication for children aged 3 years and older was approved on October 19, 2009. Fluarix Quadrivalent was approved on December 14, 2012, based on demonstration of non-inferior immunogenicity to the previously licensed trivalent formulation.

GSK proposed plans for harmonizing the monovalent bulk manufacturing process in a Type C meeting briefing package submitted on August 28, 2013. In written feedback dated September 27, 2013, CBER noted that the new process leads to an increase in nucleoprotein/neuraminidase and matrix protein for the H3N2-subtypes and requested that GSK provide data to support that this has no impact on the reactogenicity of the vaccine product. In response, GSK proposed clinical study Flu D-QIV-015, a phase 3 double-blind, randomized, active-controlled clinical trial conducted in children and adults aged ≥ 6 months to <50 years to compare the clinical immunogenicity and safety of the licensed formulation of Fluarix Quadrivalent (D-QIV LP) to the investigational formulation product produced after implementing the proposed manufacturing harmonization process (D-QIV IP).

In pre-BLA negotiations between the Applicant and CBER, during a Type C meeting held on March 11, 2014, it was agreed that children aged 6 through 35 months would not be evaluated in this supplement since this age group was not enrolled in the US and because Fluarix Quadrivalent is not approved in the US for use in this age group.

3. Clinical/Statistical

a) Clinical Program

The safety/reactogenicity and immunogenicity of Fluarix Quadrivalent, manufactured by the proposed manufacturing harmonization process, was evaluated in one clinical study (Flu D-QIV-015) in adults aged ≥ 18 to < 50 years and children aged ≥ 3 to <18 years. In addition, non-inferiority immunogenicity in children of the same age group was evaluated. The licensed formulation of Fluarix Quadrivalent was used as the active comparator in the study.

Study Flu D-QIV-015

Clinical Study Flu D-QIV-015 was a phase 3, double-blind, controlled, multi-country study conducted to evaluate the safety/reactogenicity, and immunogenicity of D-QIV LP manufactured with the new investigational process (D-QIV IP). Details on the safety and reactogenicity results from this study can be found in Section 7 below. The study consisted of 3 age cohorts: adults aged ≥ 18 to < 50 years, children aged ≥ 3 to <18 years, and children aged 6 through 35 months. As stated above, in pre-BLA negotiations, children aged 6 through 35 months were not evaluated in this supplement review because Fluarix Quadrivalent is not approved in the US at this time for use in this age group and subjects this age were not enrolled in the US. Subjects were randomized in a 1:1 ratio within each age cohort to receive either the D-QIV IP or the D-QIV LP. The randomization algorithm used a minimization procedure to minimize the imbalance between the subjects in each group over pre-defined factors.

A staggered enrollment study design was used to enroll progressively younger cohorts based on internal safety review of safety data in the older cohorts. A target of 120 and 800 subjects were to be enrolled in the adult aged ≥ 18 to < 50 years and

children aged ≥ 3 to <18 years cohorts, respectively. Vaccine-primed subjects received only 1 vaccine dose (Day 0) and vaccine-unprimed subjects received 2 doses (Day 0 and Day 28).

The primary endpoint in the adult cohort was for safety, which included local and systemic solicited adverse events (AEs) for 7 days post-vaccination, including symptoms of Oculorespiratory Syndrome (ORS) for 2 days post vaccination; and unsolicited AEs, including serious adverse events (SAEs) and deaths, for the study duration (21 days for the adult cohort).

The selected secondary endpoints included descriptive analyses of serum anti-hemagglutinin (HA) antibody titers against the 4 vaccine strains to calculate Geometric Mean Titers (GMTs) and seroprotection rates (SPRs) (Day 0 and Day 21), and seroconversion rates (SCRs) and Mean Geometric Increases (MGIs) (Day 21).

The pediatric cohort had co-primary endpoints. The safety endpoints were the same as those of adults except the study duration was longer: 28 days for influenza-primed subjects and 56 days for unprimed subjects. This included the occurrence of solicited local and systemic AEs (Days 0-6 following vaccination) in subjects aged 3 to 4 years and aged 5 through 17 years, including symptoms of ORS (Days 0-2 following vaccination), unsolicited AEs (Days 0-27 following vaccination), and Medically Attended Events (MAEs) and Serious Adverse Events (SAEs) during the entire study period in children aged ≥ 3 to <18 years.

The co-primary immunogenicity endpoint for children was immunologic non-inferiority of D-QIV IP, compared to D-QIV LP, based on hemagglutinin inhibition (HI) GMT ratios, for each of the 4 influenza vaccine strains (e.g., an upper limit (UL) of the 95% Confidence Interval [CI] for the ratio of D-QIV LP to D-QIV IP of ≤ 1.5) at 28 days after completion of the vaccination series. The pre-specified success criterion for the primary immunogenicity endpoint (UL ≤ 1.5) was met for each influenza strain. The results of immunogenicity comparison for the pediatric cohorts are summarized in Table 1.

Selected secondary endpoints for both age groups included descriptive immunogenicity evaluations for seroconversion rates (SCRs) and percent of subjects with HI titers ≥ 1:40. The adult cohort had an additional secondary endpoint assessing GMT ratios (this was a co-primary endpoint in the pediatric cohort).

There were two analysis cohorts. The Total Vaccinated Cohort (TVC) for the analysis of safety included all subjects with at least 1 vaccine administration documented. The According-to-Protocol (ATP) cohort for analysis of immunogenicity included all evaluable subjects (who met all eligibility criteria and complied with protocol procedures with no elimination criteria assigned during the study) for whom data concerning immunogenicity endpoint measures were available.

Table 1. Flu D-QIV-015 Geometric Mean Titer Ratio (D-QIV LP/D-QIV IP) of the 4 Influenza Strains in the ATP cohort

Cohort	Antibody	D-QIV LP –N	D-QIV LP - Adjusted GMT	D-QIV IP -N	D-QIV IP - Adjusted GMT	Adjusted GMT ratio	95% Lower Limit	95% Upper Limit
Children 3-17 years	A/H1N1	402	684.9	403	707.3	0.97	0.85	1.11
Children 3-17 years	A/H3N2	402	168.8	403	160.6	1.05	0.94	1.18
Children 3-17 years	B/Yamagata	402	509.4	403	496.0	1.03	0.91	1.16
Children 3-17 years	B/Victoria	402	250.4	403	240.8	1.04	0.90	1.21
Children 6-35 months	A/H1N1	424	105.3	431	98.0	1.07	0.90	1.28
Children 6-35 months	A/H3N2	423	56.3	431	47.7	1.18	1.00	1.39
Children 6-35 months	B/Yamagata	423	106.4	431	99.2	1.07	0.91	1.27
Children 6-35 months	B/Victoria	423	37.7	431	32.2	1.17	0.99	1.38

Source: Clinical Study Report for Study 201251 (Flu D-QIV-015); Tables 57 and 84

The Applicant did not evaluate immunogenic non-inferiority in the adult cohort but did provide summary statistics of the immune response shown in Table 2 below.

Table 2. Flu D-QIV-015 Summary statistics of HI titers for A/H1N1, A/H3N2, B/Yamagata, B/Victoria at Day 21 in subjects aged ≥ 18 to < 50 years using the ATP cohort for immunogenicity

Antibody	**Group**	**Day**	**N**	**S+ n''**	**S+ %**	**S+ LL 95% CI**	**S+ UL 95% CI**	**SPR n**	**SPR %**	**SPR LL 95%**	**SPR UL 95%**	**GMT Value**	**GMT LL 95% CI**	**GMT UL 95%**	**N'**	**SCR n'**	**SCR %**	**SCR LL 95%**	**SCR UL 95%**	**MGI Value**	**MGI LL 95%**	**MGI UL 95%**
Flu A/H1N1	D-QIV LP adults	0	58	51	87.9	76.7	95.0	35	60.3	46.6	73.0	53.6	36.8	78.0	-	-						
Flu A/H1N1	D-QIV LP adults	21	57	57	100	93.7	100	57	100	93.7	100	632.2	498.8	801.3	57	42	73.7	60.3	84.5	11.5	7.7	17.0
Flu A/H1N1	D-QIV IP adults	0	57	51	89.5	78.5	96.0	35	61.4	47.6	74.0	48.3	33.4	69.7	-	-						
Flu A/H1N1	D-QIV IP adults	21	57	57	100	93.7	100	56	98.2	90.6	100	655.7	493.1	871.9	57	42	73.7	60.3	84.5	13.6	8.9	20.8

Antibody	**Group**	**Day**	**N**	**S+ n’’**	**S+ %**	**S+ LL 95 % CI**	**S+ UL 95 % CI**	**SPR n**	**SPR %**	**SPR LL 95 %**	**SPR UL 95 %**	**GMT Value**	**GMT LL 95% CI**	**GMT UL 95 %**	**N’**	**SCR n’**	**SCR %**	**SCR LL 95 %**	**SCR UL 95 %**	**MGI Value**	**MGI LL 95 %**	**MGI UL 95 %**
Flu A/H3N2	D-QIV LP adults	0	58	41	70.7	57.3	81.9	14	24.1	13.9	37.2	16.0	11.9	21.5	-	-						
Flu A/H3N2	D-QIV LP adults	21	57	57	100	93.7	100	49	86.0	74.2	93.7	73.0	59.0	90.5	57	29	50.9	37.3	64.4	4.6	3.6	5.7
Flu A/H3N2	D-QIV IP adults	0	57	44	77.2	64.2	87.3	15	26.3	15.5	39.7	16.7	12.6	22.2	-	-						
Flu A/H3N2	D-QIV IP adults	21	57	57	100	93.7	100	49	86.0	74.2	93.7	80.5	63.2	102.7	57	30	52.6	39.0	66.0	4.8	3.6	6.5
Flu B/ Yamagata	D-QIV LP adults	0	58	57	98.3	90.8	100	50	86.2	74.6	93.9	101.6	76.2	135.4	-	-						
Flu B/ Yamagata	D-QIV LP adults	21	57	57	100	93.7	100	57	100	93.7	100	598.6	480.9	745.0	57	36	63.2	49.3	75.6	6.0	4.3	8.2
Flu B/ Yamagata	D-QIV IP adults	0	57	55	96.5	87.9	99.6	52	91.2	80.7	97.1	133.3	98.4	180.6	-	-						
Flu B/ Yamagata	D-QIV IP adults	21	57	57	100	93.7	100	57	100	93.7	100	591.4	475.1	736.3	57	27	47.4	34.0	61.0	4.4	3.3	6.0
Flu B/ Victoria	D-QIV LP adults	0	58	49	84.5	72.6	92.7	32	55.2	41.5	68.3	34.8	25.2	48.1	-	-						
Flu B/ Victoria	D-QIV LP adults	21	57	57	100	93.7	100	57	100	93.7	100	302.9	244.0	376.1	57	40	70.2	56.6	81.6	8.6	6.0	12.3
Flu B/ Victoria	D-QIV IP adults	0	57	54	94.7	85.4	98.9	34	59.6	45.8	72.4	38.6	29.5	50.5	-	-						
Flu B/ Victoria	D-QIV IP adults	21	57	57	100	93.7	100	57	100	93.7	100	263.4	209.0	331.9	57	36	63.2	49.3	75.6	6.8	5.0	9.2

Source: Clinical Study Report for Study 201251 (Flu D-QIV-015); Table 50
Seroconversion defined as:

- *For initially seronegative subjects, antibody titer ≥ 40 1/DIL at post-vaccination*
- *For initially seropositive subjects, antibody titer at post-vaccination ≥ 4 fold the pre-vaccination antibody titer*
- *GMT=geometric mean antibody titer calculated on all subjects*
- *MGI=geometric mean of the within-subject ratios of the post-vaccination reciprocal HI titer to the Day 0 reciprocal HI titer*
- *N =Number of subjects with results available (for seropositivity rates, SPR and GMT computation)*
- *N’=Number of subjects with both pre and post results available (for SCR and MGI computation)*
- *n’’/%= number/percentage of subjects with titer equal to or above specified value*
- *n/% = Number/percentage of seroprotected subjects*
- *n’/% = Number/percentage of seroconverted subjects*

The observed seroconversion rates (between D-QIV IP and D-QIV LP) were more similar for A/H1N1 (73.7% vs. 73.7%) and A/H3N2 (52.6% vs. 50.9%) than for B/Yamagata (47.4% vs. 63.2%) and B/Victoria (63.2% vs. 70.2%). The post-

vaccination GMT was much higher than the pre-vaccination GMT for each strain. Immunogenicity appeared generally comparable, based on secondary descriptive immunologic endpoints.

For the pediatric group, D-QIV IP met the above-defined success criteria for immunologic non-inferiority compared to D-QIV LP for all 4 influenza vaccine strains. Secondary descriptive immunogenicity results were generally comparable between both treatment arms in both primed and unprimed subjects.

A Bioresearch Monitoring (BIMO) inspection was completed at one domestic clinical study site conducting Study Flu D-QIV-015 in 41 subjects aged ≥ 3 to <18 years. A review of the inspection results did not reveal any sponsor or monitoring issues or problems that impact the data submitted in this supplement.

b) Pediatrics

Based on the criteria for the Pediatric Research Equity Act (PREA) this supplement does not meet the requirements for additional studies in children aged ≥ 6 through 35 months. When Fluarix Quadrivalent was approved in 2012 a final report for a deferred pediatric study evaluating children aged ≥ 6 through 35 months was required to be submitted by March 2014. However, two extensions were granted for this postmarketing requirement and the final report is expected to be submitted to CBER in January 2017.

c) Other Special Populations

There are insufficient data to establish whether there is a vaccine-associated risk with Fluarix Quadrivalent in pregnant women. There is no information available on the presence of Fluarix Quadrivalent in human milk, the effects on the breastfed infant, or the effects on milk production.

4. Chemistry Manufacturing and Controls (CMC)

Currently, monovalent bulks used in the manufacture of the Applicant's Flu D-TIV or Flu D-QIV vaccines are produced using different manufacturing parameters for H1N1, H3N2 and B strains. In order to simplify the manufacturing processes, the Applicant has evaluated modifications to the licensed monovalent bulk process, referred to as the "harmonized process," to reduce overall process complexity, simplify procedures, eliminate strain-specific media and components, and to make the monovalent bulk manufacturing process more robust. To support the proposed changes, information was provided on monovalent bulk consistency batches and clinical batches for the NH 2014/2015 season, produced using the harmonized process.

The drug product manufacturing process remains the same as licensed for final bulks and final containers, and the proposed harmonized monovalent bulk manufacturing process results are within the currently approved release specifications.

The focus of the harmonization process is on the process steps for (b) (4) . The following modifications have been validated for three monovalent bulk consistency batches for each of four influenza strains: (b) (4) (b) (4) .

Since the harmonization process resulted in changes to the sample matrix of the monovalent bulk, the Applicant revalidated several release-test assays all of which were found acceptable for use. This included the SRID assay which is used for potency and identity testing; determination of Polysorbate-80 by (b) (4), and determination of Octoxinol 10 by (b) (4) Bioburden, sterility and endotoxin test methods were qualified and performed in accordance with the (b) (4) and the mycoplasma testing was found to be in compliance with both the (b) (4)

a) CBER Lot Release

A review of Product Release Branch records indicate that there are no pending lots or issues that would affect approval of the submission. Since there were no revisions to the existing Fluarix Lot Release Protocol a template was not necessary.

b) Facilities Review/Inspection

Facility information and data provided in the supplement were reviewed by CBER and found to be sufficient and acceptable. The facility involved in the manufacture of drug substance is listed in the table below. The inspectional history is noted in Table 3 and is further described in the paragraph that follows.

Table 3. Drug Substance Manufacturing Facility Table for Fluarix® Quadrivalent

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification/ Results
GlaxoSmithKline Biologicals Zirkusstr. 40 Dresden, Saxony Germany	3004835618	314853925	Waived	Team Biologics May 11-19, 2015 VAI

Team Biologics performed surveillance inspections of the facility May 11-19, 2015. All 483 issues were resolved and the inspection was classified as voluntary action indicated (VAI).

c) Environmental Assessment

The supplement included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product does not alter significantly the concentration and distribution of naturally occurring substances, and no extraordinary circumstances exist that would require an environmental assessment.

5. Nonclinical Pharmacology/Toxicology

To support the toxicity profile of Fluarix Quadrivalent, with the modified manufacturing process, the Applicant submitted a repeat dose toxicity study report for D-QIV IP. This report contains adequate non-clinical toxicology data which is suitable for a safety assessment of the Fluarix Quadrivalent with the modified manufacturing process.

6. Clinical Pharmacology

No new clinical pharmacology data was required in support of this supplement.

7. Safety

The safety population for study Flu D-QIV-015 comprised 120 adults aged ≥ 18 to < 50 years and 821 children aged ≥ 3 to <18 years. For adults, the randomized 1:1 study described the reactogenicity/safety of 1 dose of D-QIV IP and 1 dose of D-QIV LP in terms of solicited AEs 7 days after vaccination, including the symptoms of ORS over 3 days post-vaccination, and in terms of unsolicited AEs 21 days after vaccination. For children, the study described the reactogenicity/safety of D-QIV IP and D-QIV LP in terms of solicited AEs 7 days after vaccination, including the symptoms of ORS over 3 days post-vaccination; and in terms of unsolicited AEs, 28 days after vaccination. Medically Attended Events (MAEs) and Serious Adverse Events (SAEs) were evaluated in both cohorts during the entire study period. Safety and reactogenicity were summarized using descriptive statistics. Safety was assessed in the TVC.

Local and systemic solicited AEs:

Rates of certain solicited local AEs (pain, swelling) and systemic AEs (fatigue, pain, headache, joint pain, myalgia) were numerically higher among adults in the D-QIV IP group compared with D-QIV LP; the frequencies of AEs categorized as grade 3 were low (1 of 59-60 subjects). The reactogenicity of D-QIV IP was within the range of AEs rates reported for other vaccines recommended by the ACIP for routine use in adults. However, the numbers enrolled (N= 60 per arm) were small, such that these differences are unlikely to be clinically meaningful. A similar trend was not observed among children aged ≥ 3 to <18 years which included a larger sample size (N = 402 for D-QIV LP and N = 403 for D-QIV IP).

During the 7-day post vaccination period, in the adult group, the most frequently reported local solicited AE was pain (54.2% [32/59] versus 68.3% [41/60] of the subjects in the D-QIV LP

and D-QIV IP groups, respectively). There were no grade 3 solicited local AEs reported in the D-QIV LP group; one subject in the D-QIV IP group reported a grade 3 local solicited AE (pain).

The most frequently reported solicited systemic AEs were fatigue (reported by 33.9% [20/59] in the D-QIV LP group and 53.3% [32/60] in the D-QIV IP group), headache (reported by 27.1% [16/59] in the D-QIV LP group and 50.0% [30/60] in the D-QIV IP group) and myalgia (reported by 22.0% [13/59] in the D-QIV LP group and 35.0% [21/60] in the D-QIV IP group). The incidence of grade 3 solicited general AEs were low in both groups and did not exceed 1.7% for any of the groups.

In the 7-day post vaccination period, 3.4% [2/59] subjects in the D-QIV LP group and 3.3% [2/60] of subjects in the D-QIV IP group experienced fever, none of which were grade 3 or higher (> 39.0°C).

In the pediatric group, during the 7-day follow-up period after vaccination, pain was the most frequently reported solicited local AE 61.7% [253/410] versus 59.3% [243/410] of subjects after Dose 1 in the D-QIV LP and D-QIV IP groups, respectively; 39.4% [39/99] versus 35.0% [36/103] of subjects after Dose 2 in the D-QIV LP and D-QIV IP groups, respectively). Pain of grade 3 intensity after Dose 1 was reported for 4.9% [20/410] versus 3.4% [14/410] of subjects in the D-QIV LP and D-QIV IP groups, respectively. After Dose 2, 2.0% [2/99] of subjects in the D-QIV LP group reported grade 3 pain versus none in the D-QIV IP group. The incidence of swelling and redness was similar in both groups after Dose 1 and after Dose 2. Post-dose 1 swelling was 24.4% (100/410) and 24.9% (102/410) of subjects in the Fluarix-LP and Fluarix-IP groups, respectively; post-dose 1 redness was 29.0% (119/410) and 28.8% (118/410) of subjects in the Fluarix-LP and Fluarix-IP groups, respectively; post dose 2 swelling was 17.2% (17/99) and (16/103) 15.5% of subjects in the Fluarix-LP and Fluarix-IP groups, respectively; post-dose 2 redness was 21.1% (21/99) and 24.3 (25/103) of subjects in the Fluarix-LP and Fluarix-IP groups, respectively. The incidence of grade 3 redness or swelling after Dose 1 and after Dose 2 did not exceed 2.0% [8/410] in any of the groups.

In children aged 3 to 4 years, the most frequently reported solicited general AE was loss of appetite (19.4% [14/72] in the D-QIV LP group versus 12.9% [9/70] in the D-QIV IP group; drowsiness (20% [14/70] versus 9.7% [7/72] in the D-QIV IP group and D-QIV LP groups, respectively.) The incidence of grade 3 solicited general AEs did not exceed 4.2% [3/72]. During the same period, the incidence of fever ≥ 38°C (100.4°F) was 9.7% [7/72] versus 5.7% [4/70] of subjects in the D-QIV LP and D-QIV IP groups, respectively. Fever > 39°C (102.2°F) was reported in 4.2% [3/72] versus 1.4% [1/70] of subjects in the D-QIV LP and D-QIV IP groups, respectively.

In children aged 5 through 17 years, the most frequently reported solicited general AE during the 7-day follow-up period after Dose 1, fatigue (29.3% [99/338]) versus 27.6% [94/340] of subjects in the D-QIV LP and D-QIV IP groups, respectively), headache (22.5% [76/338] versus 24.1% [82/340] of subjects in D-QIV LP and D-QIV IP groups, respectively) and myalgia (24.9% [84/338] versus 20.6% [70/340] of subjects in D-QIV LP and D-QIV IP groups, respectively).

The incidence of grade 3 solicited general AEs did not exceed 3.8% [13/338] for any group and overall did not increase after Dose 2 in any of the treatment groups.

ORS-like symptoms:
In adults, 11.8% [7/59] and 18.3% [11/60] of subjects in the D-QIV LP and D-QIV IP groups, respectively, had at least one ORS-like symptom. During the 3-day post-vaccination period, sore throat was the most frequently reported ORS-like symptom (3.4% [2/59] versus 6.7% [4/60] of subjects in the D-QIV LP and D-QIV IP groups, respectively), followed by cough (3.4% [2/59] versus 5.0% [3/60] of subjects in the D-QIV LP and D-QIV IP groups, respectively). Only one subject in each group reported red eyes post vaccination. No chest tightness, difficulty of breathing, swelling of the face or wheezing was reported.

In children, 25.1% (103/410) and 21.7% (89/410) of subjects in the D-QIV LP and D-QIV IP groups, respectively, had at least one ORS-like symptom. During the 3-day post-vaccination period, after Dose 1 in the pediatric group, cough was the most frequently reported ORS-like symptom (7.6% [31/410] versus 8.5% [35/410] of subjects in the D-QIV LP and D-QIV IP groups, respectively.) After Dose 2, cough was reported by 13.1% [13/99] versus 5.8% [6/103] of subjects in the D-QIV LP and D-QIV IP groups, respectively.

Unsolicited AEs:
In the adult group, during the 21-day post-vaccination period, at least one unsolicited AE was reported for 23.3% [14/60] of subjects each in the D-QIV LP and D-QIV IP groups. The most frequently reported unsolicited AEs, were nasopharyngitis in the D-QIV LP group (6.7% [4/60]) and headache in the D-QIV IP group (3.3% [2/60]). The incidence of grade 3 unsolicited AEs was low in both groups; 3.3% [2/60] in the D-QIV LP group and 5.0% [3/60] in the D-QIV IP group.

In the pediatric group, during the 28-day follow-up post-vaccination, at least one unsolicited AE was reported in 20.9% [86/411] versus 20.2% [83/410] of subjects in the D-QIV LP and D-QIV IP groups, respectively. Upper respiratory tract infection was the most frequent in both groups, 4.1% [17/411] versus 3.2% [13/410], of subjects in the D-QIV LP and D-QIV IP groups, respectively. The incidence of grade 3 unsolicited AEs was similar in both groups, 1.9% [8/411] versus 2.9% [12/410], of subjects the D-QIV LP and D-QIV IP groups, respectively).

MAEs:
In adults, at least one unsolicited MAE was reported for 13.3% [8/60] of subjects in the D-QIV LP group and for 15.0% [9/60] of subjects in the D-QIV IP group. The incidence of grade 3 MAEs was 1.7% [1/60] in the D-QIV LP group and 5.0% [3/60] in the D-QIV IP group. The symptoms were bronchitis, post-procedural inflammation, intervertable disc protrusion, and spinal disorder. None were assessed as causally related to the vaccination.

In children, at least one unsolicited MAE was reported for 12.7% [52/411] of subjects in the D-QIV LP group versus 14.4% [59/410] of subjects in the D-QIV IP group. At least one grade 3 MAE was reported by 1.5% [6/411] of subjects in the D-QIV LP group versus 1.7% [7/410]

of subjects in the D-QIV IP group. There were no reports of grade 3 MAEs with causal relationship to vaccination reported in this cohort during the study period.

Nonfatal Serious Adverse Events (SAEs)

There were three nonfatal SAEs reported:

- One case of inflammation post-hysterectomy in a 41-year old female who received D-QIV LP. The event occurred on study day 1 and lasted 13 days, with complete resolution.
- One case of back pain secondary to lumbar spine syndrome in a 22-year old female who received D-QIV IP. The event occurred on study day 16 and lasted 10 days with complete resolution.
- One case of viral meningitis in a 5-year old boy who received D-QIV IP. The event occurred on study day 18 and resolved completely after 7 days.

The CBER review team concurred with the investigator assessment that a causal relationship between these events and vaccination was unlikely.

Deaths

There were no deaths during the study.

There were no safety imbalances noted in either solicited or unsolicited AEs and no SAEs that appeared related to study product. The safety profile of the vaccine manufactured by investigational manufacturing processes was similar to the licensed product and found acceptable.

8. Advisory Committee Meeting

A Vaccines and Related Biologics Products Advisory Committee (VRBPAC) meeting was not held for this supplement, as there were no issues or concerns that presented during the course of review of the supplement that required consult from the advisory committee.

9. Other Relevant Regulatory Issues

There are no additional relevant regulatory issues in addition to the discussions in this memo.

10. Labeling

To comply with the 2014 Final Rule, *Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling,* also known as the Pregnancy and Lactation Labeling Rule (PLLR), a request was made to the Applicant to submit a Package Insert (PI) to include language to comply with the PLLR. The proposed Fluarix Quadrivalent PI was reviewed by clinical and toxicology reviewers and revisions were made to Section 8, Use in Specific Populations, based on CBER recommendations.

In Section 6.1, Clinical Trials Experience, CBER recommended that the Applicant modify Table 2 to Table 5, in the submission, to include the percentage of subjects who experienced a grade 3 or higher AE in addition to the percentage of subjects who experienced the AE overall.

The committee concurred that the Final Draft Label submitted on November 8, 2016 is acceptable.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The data submitted by the Applicant to this supplement support approval of Fluarix Quadrivalent containing bulk monovalent antigens produced via the newly-harmonized manufacturing process. The Indication, for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine in persons aged 3 years and older, remains unchanged.

b) Risk/ Benefit Assessment

The risk-benefit profile for the use of Fluarix Quadrivalent is favorable. The changes to the manufacturing process have not changed the risk-benefit assessment for the product.

c) Recommendation for Postmarketing Activities

Routine pharmacovigilance monitoring remains adequate for Fluarix Quadrivalent as the bulk monovalent antigens, produced via the newly harmonized manufacturing process, and the Indication for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine in persons aged 3 years and older, remains unchanged.

The applicant agreed to a non-506B postmarketing commitment to perform one cleaning validation run (b) (4) and to submit the cleaning validation summary report by June 2017.

Concurrence Page

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