Summary Basis of Regulatory Action

Date: January 11, 2018
From: Goutam Sen, Ph.D., Chair of the Review Committee
BLA/ STN#: 125127/834

Applicant Name: GlaxoSmithKline's Biologicals

Date of Submission: March 15, 2017
PDUFA Goal Date: January 12, 2018

Proprietary Name: Fluarix® Quadrivalent
Established Name: Influenza Vaccine

Indication: Fluarix Quadrivalent is a vaccine indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine for use in persons 6 months and older.

Recommended Action: Approval

Signatory Authorities Action: Approval

Offices Signatory Authority: Wellington Sun, M.D., Director, DVRPA

☐ **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.**

The table below indicates the material reviewed when developing the SBRA.

Document title	**Reviewer name, Document date**
Clinical Review	Susan Wollersheim, M.D., 10/29/2017
Statistical Review	Charles Cheung, Ph.D., 12/01/2017
Bioresearch Monitoring Review	Carla Jordan, 12/01/2017
Labeling – APLB review	Sonny Saini, 11/27/2017
Product Review	Zhiping Ye, Ph.D., 11/27/2017
Assay Review	Charles Cheung, Ph.D., 12/01/2017
Pharmacovigilance Review	Wenyu Sun, M.D., 12/06/2017

Cross referenced applications:

- IND 14473, Influenza Virus Quadrivalent Purified Hemagglutinin (2010/2011 A/A/B strains plus B Yamagata; embryonated hen's eggs: Fluarix process) Vaccine (Flu D-QIV)
- BLA 125127/513, To include a quadrivalent influenza virus vaccine formulation (Fluarix Quadrivalent) for the prevention of influenza disease in persons 3 years of age or older caused by influenza viruses contained in the vaccine.

- BLA 125163/775, To include clinical data to support harmonization of the monovalent bulk manufacturing process for the Dresden manufacturing facility.

1. Introduction

Fluarix Quadrivalent formulation (referred as D-QIV throughout this document) is a split virion, quadrivalent seasonal influenza vaccine (QIV), contains the purified outer membrane protein hemagglutinin (HA) from each of the 4 influenza virus strains recommended annually by the World Health Organization (WHO) and the Vaccines and Related Biological Products Advisory Committiee (VRBPAC). The Fluarix Quadrivalent HA antigens are derived from viruses propagated in embryonated chicken eggs and are presented as a suspension for injection, in prefilled syringes as a 0.5 mL dose (without thimerosal). Each dose contains 60 micrograms (mcg or µg) HA in the recommended ratio of 15 mcg HA of each of the 4 influenza strains in a sterile, buffered aqueous suspension.

GlaxoSmithKline's Biologicals (referred as GSK throughout this document) submitted this supplemental Biologics Licensing Application (sBLA) on March 15, 2017, to support use of D-QIV in children 6 to 35 months based on safety, immunogenicity and efficacy data from a Phase 3 clinical study, FLU-D-QIV-004. This study describes a clinical efficacy trial evaluating the safety and immunogenicity of D-QIV were compared to non-influenza vaccine controls (Havrix: Hepatitis A vaccine; Varilrix/Varivax/ProVarivax: varicella vaccine or Prevnar 13: pneumococcal polysaccharide conjugate vaccine, depending on the subjects age and priming status) in children 6 to 35 months of age. D-QIV was administered as a 0.5mL dose containing 60µg of HA (15µg of each of the four vaccine strains). In the comparator arm, children were administered the comparator non-influenza virus vaccine. Revised labeling for D-QIV formulation was also provided with this supplement.

2. Background

Influenza is an acute, highly contagious, respiratory disease condition caused by influenza viruses, mainly spread through respiratory droplets. The illness is accompanied by fever and variable degrees of other systemic symptoms, ranging from mild fatigue to respiratory failure and even death. In the United States (U.S.), influenza is estimated to cause 200,000 hospitalizations each year. The highest risk of complications occur among young children and in particular children younger than 2 years, adults aged 65 years or older, pregnant women, and people of any age with underlying chronic conditions that put them at risk for influenza disease.

Influenza A and B viruses cause annual epidemics of respiratory illness and are a significant cause of pediatric morbidity and mortality. In the U.S., an estimated 20,000 children under 5 years of age are hospitalized annually due to influenza complications[1]. In addition, since 2004, the annual number of reported laboratory-confirmed influenza-associated pediatric deaths in the U.S. has ranged from 34 to 171 per season and 358 during the 2009 H1N1 pandemic[2]. The highest influenza burden in terms of pediatric respiratory admissions is seen in infants 6 to 11 months of age[3] and rates of illness in children younger than 2 years of age are substantially higher than those in children 2 years of age or older[4, 5].

Fluarix was licensed in the U.S. on August 31, 2005, for the prevention of influenza subtypes A and type B contained in the vaccine under the accelerated approval regulations. The

approval was based on the immune response elicited by Fluarix in clinical studies in adults 18 through 49 years of age. Since products approved under the accelerated approval regulation 21 CFR 314.510 require further studies that are adequate and well controlled to verify and describe clinical benefit, a clinical endpoint efficacy study (Fluarix-US-006 in 2007) was conducted in adults 18 through 49 years of age. The efficacy of Fluarix was confirmed in this clinical endpoint study and 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 (STN 125127/319).

Fluarix Quadrivalent (D-QIV) formulation was approved on December 14, 2012, under STN 125127/513 for use in persons 3 years of age and older. A PREA postmarketing requirement was included in the approval letter for conducting a study to evaluate the safety and immunogenicity of D-QIV in children 6 to 35 months of age. During review of initial submission of GSK's pediatric clinical study protocol FLU D-QIV 004 in March 2011, CBER expressed concerns about GSK's proposal to use moderate to severe influenza (defined as a subset of influenza disease with any of the following: fever >39°F, physician-diagnosed acute otitis media, physician-diagnosed lower respiratory tract illness, physician-diagnosed serious extra-pulmonary complications, hospitalization in the intensive care unit, or supplemental oxygen required for more than 8 hours) as a primary endpoint, because GSK's definition included an aggregate of medical conditions that differ widely in severity (fever vs. encephalitis). During a Type-A meeting between CBER and GSK in June 2011, CBER re-emphasized the concern about the usefulness of moderate to severe disease as a study endpoint. After several discussions between CBER and GSK (related to the review of the protocol under IND: 14473), agreement about the sample size, safety and immunogenicity endpoints for this study, FLU D-QIV-004, was reached. After several modifications, GSK finalized the FLU D-QIV-004 protocol under the IND 14473, completed the study, and submitted the clinical study report to the IND on January 18, 2017, to fulfill the postmarketing study commitment.

In this submission, GSK proposes to update the D-QIV Prescribing Information (PI) to lower the minimum age indication from 3 years of age to 6 months of age, and to include efficacy, immunogenicity, and safety data generated in children 6 to 35 months of age. GSK has submitted the results of the pivotal efficacy study FLU D-QIV-004 (hereafter referred to as D-QIV-004) conducted in 6 to 35 month-old children, as well as results from two supportive studies, FLU D-QIV-009 (hereafter referred to as D-QIV-009) and FLU D-QIV-015 (hereafter referred to as D-QIV-015).

D-QIV-004 study was a Phase 3, observer-blind, randomized, multi-country, multi-center, comparator study with parallel treatment groups conducted from October 01, 2011 to December 31, 2014. The study was designed to demonstrate the efficacy and safety of D-QIV in children 6 to 35 months of age. Subjects were randomized 1:1 to receive either D-QIV or non-influenza vaccine control.

D-QIV-009 was a Phase 3, open-label, multi-country, multi-center, active controlled study (extension of study D-QIV-004, Cohort 1) to evaluate the immunogenicity, safety and reactogenicity of a revaccination dose. This was a Non-IND revaccination descriptive study

conducted to comply with EU Pediatric Investigational Plan. A key goal of study D-QIV-009 was to evaluate whether the administration of one dose of D-QIV in children 17-48 months of age who had received 2 doses of D-QIV one year earlier (i.e. primed) in study D-QIV-004 (Cohort 1) mounted an antibody response 7 days post-vaccination in study D-QIV-009, compared to children who had received 2 doses of non-influenza vaccine in study D-QIV-004 (i.e. unprimed). Vaccine-primed subjects received 1 injection of D-QIV at Day 0 and vaccine-unprimed subjects received 2 doses of D-QIV, one dose at Day 0 and one dose at Day 28.

Study D-QIV-015 was a Phase 3, double-blind, randomized, controlled, multi-country study, to assess safety and immunogenicity of D-QIV manufactured with the harmonized monovalent bulk process. Three independent age groups were assessed (18-49 years, 3-17 years, 6-35 months) each with their own set of objectives. In this submission, GSK has only provides data pertaining to the 6-35 months group, as this data serves as an immunogenicity and safety bridge for D-QIV manufactured with the harmonized process (D-QIV IP) and D-QIV manufactured with the previous process that was used in D-QIV-004 and D-QIV-009 (D-QIV LP). Complete study report for D-QIV-015 was previously submitted to CBER on January 21, 2016, and was reviewed under STN 125127/775 (approved on November 18, 2016). Within each age cohort, subjects were randomized 1:1 to receive either D-QIV IP or D-QIV LP. The results for the D-QIV-015 study in 6-35 month cohort are briefly described in this submission because they support the extrapolation of the D-QIV-004 and D-QIV-009 study data generated with D-QIV LP from 2011-2014 to D-QIV IP manufactured according to the current harmonized process.

3. Chemistry Manufacturing and Controls (CMC)

No new manufacturing changes are proposed in this supplement.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology studies were performed in support of this supplement.

5. Clinical Pharmacology

No new clinical pharmacology information was provided in this supplement.

6. Clinical/ Statistical/Pharmacovigilance

a) Clinical Program

All studies were conducted under US IND 14473 with the exception of study D-QIV-009 (completed to comply with the EU pediatric investigation plan) for which the clinical study report was provided after study completion to the IND, as the results were considered of interest.

The primary efficacy and safety data to support use of D-QIV formulation in the requested age indication was collected from one Phase 3 clinical trial conducted in children ages ≥ 6 to < 36 months, study D-QIV-004. However, two additional studies, D-QIV-009 and D-QIV-015 are described briefly in this submission (summarized in Table-1). The data from these two studies were evaluated in the integrated summary of safety, primarily for important safety signals such as SAEs and deaths, as discussed in the Safety section below.

Table 1. Summary of Primary Study D-QIV-004 and 2 Supportive Studies Evaluating Fluarix-QIV in Healthy Children Ages 6 through 35 Months.

Study number (NCT number)	Countries	Study design[1]	Treatment arms (N[2])
D-QIV-004 (NCT01439360)	Bangladesh, Belgium, Czech Republic, Dominican Republic, Honduras, India, Lebanon, Philippines, Poland, Spain, Thailand, Turkey, UK	Phase 3, observer-blind, randomized, non-influenza vaccine comparator-controlled study	D-QIV[3] (6006) Non-influenza vaccine comparator (6012)
D-QIV-009 (NCT01702454)	Czech Republic, Poland, Spain, UK	Phase 3, observer-blind, randomized, active-controlled study	Vaccine-primed 1 dose D-QIV (241) Vaccine-unprimed (control) 2 doses D-QIV (229)
D-QIV-015 (NCT0220713)	Bangladesh, France, Germany, Spain, Poland	Phase 3, double-blind, randomized, active-controlled study	D-QIV-IP (466) D-QIV-LP (474)

Source: Adapted from BLA 125127/834.0, m2.5 Clinical Overview, Table 1
[1]In all studies primed subjects received a single intramuscular (IM) dose of the study product on day 0 and unprimed subjects (those who had not received prior seasonal influenza vaccination) received two IM doses of study product 28 days apart.
[2]N: total vaccinated cohort
[3]QIV: quadrivalent

Study D-QIV-004 was a phase 3, observer-blind, randomized, multi-country, non-influenza vaccine comparator-controlled study to demonstrate the efficacy of GSK's quadrivalent seasonal influenza candidate vaccine GSK2321138A (Fluarix Quadrivalent; D-QIV), administered intramuscularly in children 6 to 35 months of age (mean age: 22 months; 51% were male; 27% were white, 45% were Asian, and 28% were of other racial/ethnic groups).

The primary objectives were:

1) To evaluate the efficacy of D-QIV in the prevention of reverse transcription polymerase chain reaction (RT-PCR) confirmed moderate to severe influenza A and/or B disease due to any seasonal influenza strain, when compared to non-influenza vaccine controls in children aged 6 to 35 months and

2) To evaluate the efficacy of D-QIV in the prevention of RT-PCR confirmed any severity influenza A and/or B disease due to any seasonal influenza strain, when compared to non-influenza vaccine controls in children aged 6 to 35 months.

Secondary objectives were to evaluate the efficacy of D-QIV in the prevention of:

1) lower respiratory illness (LRI) associated with RT-PCR confirmed influenza A and/or B, when compared to non-influenza vaccine controls,

2) culture confirmed moderate to severe influenza A and/or B disease due to antigenically-matching influenza strains when compared to non-influenza vaccine controls,
3) culture confirmed influenza A and/or B disease of any severity due to antigenically-matching influenza strains when compared to non-influenza vaccine controls,

4) culture confirmed moderate to severe influenza A and/or B disease due to any seasonal influenza strain, when compared to non-influenza vaccine control,

5) culture confirmed influenza A and/or B disease of any severity due to any seasonal influenza strain, when compared to non-influenza vaccine controls,

6) acute otitis media (AOM) associated with RT-PCR confirmed influenza A and/or B, when compared to non-influenza vaccine controls and

7) RT-PCR confirmed severe influenza A and/or B disease, when compared to non-influenza vaccine controls.

Of the 12046 subjects enrolled, 12018 were vaccinated [Total Vaccinated Cohort (TVC)], among them 6006 received D-QIV and 6012 received non-influenza vaccine comparator achieving a 1:1 ratio. The study was conducted at 106 sites in 13 countries: Bangladesh, Belgium, Czech Republic, Dominican Republic, Honduras, India, Lebanon, Philippines, Poland, Spain, Thailand, Turkey, UK over five influenza seasons in five independent cohorts. Study Cohorts and corresponding countries and dates are described in Table 2 below. The demographic characteristics were similar between the two treatment groups.

Table 2. Study D-QIV-004. Cohorts, Countries, and Study Dates

Cohort	Countries	Study Dates
1	Belgium, Czech Republic, Poland, Spain, United Kingdom	October 01, 2011 to July 07, 2012
2	Bangladesh, Dominican Republic, Honduras	March 29 to December 12, 2012
3	Belgium, Czech Republic, Lebanon, Poland, Spain, Turkey, United Kingdom	October 08, 2012 to July 16, 2013
4	Bangladesh, Dominican Republic, Honduras, Philippines, Thailand	March 06 to December 02, 2013
5	Bangladesh, Dominican Republic, Honduras, India, Philippines, Thailand	March 11 to December 31, 2014

Source: Adapted from STN 125127/834.0; FLU D-QIV 004 Clinical Study Report; Tables 6 and 22.

All subjects < 12 months of age were considered vaccine-unprimed. D-QIV was administered as a 0.5mL dose intramuscular (IM) injection containing 60µg of HA (15µg of each of the four vaccine strains). Vaccine-primed subjects included all subjects who had previously received at least two doses of influenza vaccine, separated by 28 days. Vaccine-unprimed subjects included all subjects who had previously not received two doses of influenza vaccine, separated by at least 28 days. The non-influenza vaccine controls were based on age and vaccine priming status as follows: for subjects < 12 months of age, two doses of Prevnar13 were administered as 0.5mL dose IM injections 28 days apart. For subjects ≥12 months of age considered vaccine-primed, the US licensed formulation of Havrix was administered as a 0.5mL IM injection. For subjects ≥12 months of age considered vaccine-unprimed, one dose of Havrix was administered as dose 1 and 28 days later, one dose of either US licensed Varivax/ProVarivax (0.5mL dose IM injection) or non-US licensed Varilrix (0.5mL dose subcutaneous injection) was administered. For the efficacy assessment, all subjects were followed through active and passive surveillance for influenza like illness (ILI; defined as a temperature ≥ 38.0°C and at least one of the following symptoms: cough, runny nose, nasal congestion or breathing difficulty) to obtain a nasal swab specimen for influenza testing. For the immunogenicity assessment, a subset of subjects had blood samples taken on Day 0 (baseline) and 28 days after completion of the vaccine series (Day 28 for vaccine-primed subjects and Day 56 for vaccine-unprimed subjects) to assess immune response and for evaluation of HAI titers.

The According to protocol time to event cohort for analysis of efficacy (ATP-E-Time to event cohort) included all eligible subjects from the TVC with completed scheduled vaccination who met all inclusion and exclusion criteria for the study, who had received study vaccine(s) according to their random assignment, for whom administration site of study vaccine was known, and who started their influenza surveillance period. Subjects who met criteria for elimination or exclusion from the According to Protoocol (ATP) analysis were censored at the time of the occurrence of the event and were not eliminated. The ATP-E-Time to event cohort consisted of 11404 subjects (5707 in the D-QIV group and 5697 in the control group). The ATP cohort for analysis of immunogenicity included all evaluable subjects from the TVC. The ATP cohort for immunogenicity consisted of 1332 subjects (753 in the D-QIV group and 579 in the control group). Out of the 1332 subjects in the ATP cohort for immunogenicity, 132 subjects (59 D-QIV and 73 control) were included from Cohort 1, 538 (353 D-QIV and 185 control) from Cohort 2, 120 subjects (66 D-QIV and 54 control) from Cohort 3, 241 subjects (127 D-QIV and 114 control) from Cohort 4, and 301 subjects (148 D-QIV and 153 control) from Cohort 5.

The two parallel primary endpoints and the criteria for success for each of the primary endpoints for study D-QIV 004 were as follows: i) first occurrence of RT-PCR confirmed moderate to severe influenza A and/or B disease due to any seasonal influenza strain during the influenza surveillance period with criteria for success defined as if the lower limit (LL) of the two-sided 97.5% Confidence Interval (CI) of vaccine efficacy (VE) was above 25% and ii) first occurrence of RT-PCR confirmed influenza A and/or B disease of any severity due to any seasonal influenza strain during the influenza surveillance period with criteria for success defined as if the LL of the two-sided 97.5% CI of VE was above 15%. The vaccine efficacy (VE) for the prevention of RT-PCR confirmed moderate to severe influenza A and/or B

disease due to any seasonal strain in comparison to non-influenza vaccine controls in children 6 to 35 months was 63.2%; the lower limit (LL) of the two-sided 97.5% confidence interval (CI) was 51.8%. The VE for prevention of RT-PCR confirmed influenza A and/or B disease of any severity due to any seasonal strain, when compared to non-influenza vaccine controls in children 6 to 35 months, was 49.8 %; LL of the two-sided 97.5% CI was 41.8%.

The first six of the seven sequential secondary endpoints met the pre-specified statistical criteria. The VE of D-QIV for the prevention of culture confirmed influenza A and/or B of any severity due to antigenically-matching influenza strains was 60.1 %. A summary of immunogenicity by HI antibody Geometric Mean Hemagglutination Inhibition Antibody Titers (GMT) against influenza vaccine strains and Seroconversion rates (SCR) are displayed below in Table 3.

Table 3. Study D-QIV-004. Geometric Mean Hemagglutination Inhibition Antibody Titers Against Influenza Vaccine Strains and Seroconversion rates 28 days after Last Vaccination (ATP cohort for immunogenicity)

		GMT[1]		SCR[2]	
Influenza Strain	Group	N[3]	Value	N	n (%)[4]
Flu A (H1N1) HI	D-QIV	752	165.3	743	596 (80.2)
	Control	578	12.6	566	20 (3.5)
Flu A (H3N2) HI	D-QIV	753	132.1	746	513 (68.8)
	Control	578	14.7	567	24 (4.2)
Flu B (Victoria) HI	D-QIV	750	92.6	742	514 (69.3)
	Control	579	9.2	567	5 (0.9)
Flu B (Yamagata) HI	D-QIV	753	121.4	745	605 (81.2)
	Control	579	7.6	568	13 (2.3)

Source: Adapted from STN 125127/834: FLU D-QIV 004 Clinical Study Report, Table 61.
[1]GMT: geometric mean antibody titer calculated on all subjects
[2]Seroconversion rate (SCR) 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
[3]Number of subjects with results available; for SCR, both pre and post results
[4]n/%:number/percentage of seroconverted subjects

In general, vaccine efficacy and immunogenicity were lower in the younger cohort (6 to 11 months); however, the study was not powered to detect significant differences between age groups and this age group had the lowest number of enrolled subjects when compared to those in the 6 through 17 month or 18 through 35 month age groups. Among subjects between 6 and 11 months of age, vaccine efficacy for the RT-PCR confirmed influenza of any severity was 19.2% (95% CI: -29.3%, 49.9%), VE for subjects between 6 and 17 months of age was 43.3% (95% CI: 27.8%, 55.8%) and VE for subjects between 18 and 35 months of age was 51.6% (95% CI: 43.7%, 58.4%).

Study D-QIV-009 was a Phase 3, open-label, multi-country (Czech Republic, Poland, Spain, UK), multi-center, active controlled study (extension of study D-QIV-004, Cohort 1) to evaluate the immunogenicity, safety and reactogenicity of a revaccination dose administered to vaccine-primed and vaccine-unprimed children aged 17-48 months who previously participated in Cohort 1 of study D-QIV-004. Subjects were enrolled to the following groups: i) vaccine-primed (received 2 doses of D-QIV in study D-QIV-004 and received 1 dose of D-

QIV in this study): 224 children (ATP cohort for immunogenicity) and ii) vaccine-unprimed (received 2 doses of a non-influenza vaccine in study D-QIV-004 and received 2 doses of D-QIV in this study): 209 children (ATP cohort for immunogenicity). A total of 470 subjects were enrolled and received at least one vaccine dose. The early and robust revaccination response (in terms of seropositivity, SPR, SCR, GMT, and GMI, measured 7 days after revaccination) demonstrated that 2 primary doses of D-QIV in study D-QIV-004 established immune memory in children 6-35 months of age that could be recalled in vaccine-primed subjects, but not in the vaccine-unprimed subjects [SCR of 76.2% to 93.8% with a LL of 95% CI of 69.8% to 89.6%, (ATP-I excluding subjects with a RT-PCR confirmed influenza infection from study D-QIV-004) but not in the vaccine-unprimed subjects (SCR of 28.3% to 38.2% with a LL of 95% CI of 21.7% to 30.9%)]. Of note, the immune response was observed for the A/H1N1 and B/Victoria strains that were present in both the primary and subsequent year vaccines, as well as for the A/H3N2 and B/Yamagata strains that changed in the subsequent year vaccine, suggesting cross-priming for these two unmatched strains. The HI antibody response elicited by a 2-dose priming schedule in the parent study persisted up to a year as evidenced by higher Day 0 (pre-revaccination) GMTs for the 2 priming strains common with the revaccination strains (A/H1N1 and B/Victoria) in the vaccine-primed group compared to the vaccine-unprimed group. A similar pattern of immunogenic responses (as summarized above), in terms of neutralizing and anti-neuraminidase antibody immune response, was observed for both ATP immunogenicity cohorts.

Study D-QIV 015 was a phase 3 double blind, 1:1 randomized study comparing the D-QIV manufactured with the previous process that was used in D-QIV-004 and D-QIV-009 (D-QIV LP) to D-QIV manufactured with the harmonized process (D-QIV IP). For subjects aged 6 through 35 months, the study was conducted in five countries (Bangladesh, France, Germany, Spain, and Poland) and enrolled consented eligible subjects that included those with chronic medical conditions predisposing to a risk of influenza complications (these subjects were excluded from Study D-QIV 004).

The primary immunogenicity endpoint for subjects 6 through 35 months of age was to demonstrate non-inferiority of D-QIV IP as compared to D-QIV LP in terms of HI GMT's and GMT ratio for each of the vaccine influenza strains at 28 days after completion of the vaccination series. The total vaccinated cohort consisted of 940 subjects (466 in the D-QIV IP group and 474 in the D-QIV LP group). The According to Protocol cohort for analysis of efficacy – time to event group consisted of 859 subjects (432 in the D-QIV IP group and 427 in the D-QIV LP group).

The primary immunogenicity endpoint for subjects 6 through 35 months of age, was met as shown by the demonstration of immunological non-inferiority of FLU D-QIV-IP to FLU D-QIV-LP at day 28 after completion of the vaccination series, with the UL of the 95% CI of the GMT ratio D-QIV-LP/IP was ≤ 1.5 for each of the vaccine strains. The HI GMTs ranged from 32.1 to 100.8 in the FLU Q-QIV-IP group and from 38 to 105.5 in the D-QIV-LP group across all 4 strains. The FLU D-QIV-IP group had a seroconversion rate of $\geq 49.4\%$ and the FLU D-QIV-LP had a seroconversion rate of $\geq 49.9\%$.

Subgroup Analyses

The summary statistics for demographic variables were comparable between the D-QIV and control groups in the ATP efficacy - Time to event cohort, ATP cohort for efficacy, TVC, and ATP cohort for immunogenicity, and immune subset for (b) (4) and (b) (4) testing cohorts. The study was not powered to detect differences in efficacy, immunogenicity or safety with regard to gender or geographical ancestry. Post-hoc analyses suggested efficacy, immunogenicity and safety to be comparable across both genders and across geographic ancestry (White/Caucasian, Asian, Others) for children 6 through 35 months of age.

b) Pediatrics

Fluarix-TIVand D-QIV are currently approved for use in persons ages 3 years and older. The approval letter for STN 125127/513 (initial approval of D-QIV in persons ages 3 years and older) established Postmarketing Requirements that required GSK to conduct a Pediatric Research Equity Act (PREA) clinical study to evaluate the safety and immunogenicity of D-QIV in children 6 to 35 months of age as a post marketing requirement. GSK has conducted the study and submitted the results in this supplement. The purpose of this sBLA 125127/834 is to extend the age indication to ages 6 months and older. During the review of STN 125127/513, GSK received a partial waiver for infants <6 months of age based on the reasoning that Fluarix and D-QIV would provide no meaningful therapeutic benefit over vaccination beginning at 6 months of age, and these vaccines are unlikely to be used by a substantial number of infants <6 months of age (Section 505B(a)(4)(A)iii of the Food Drug and Cosmetic Act). The study results were discussed during August 31, 2016, PeRC meeting and the committee agreed that this supplement fulfilled the deferred pediatric study under PREA for active immunization for the prevention of disease caused by Influenza A subtype viruses and type B viruses contained in D-QIV in the pediatric population 6 months to <3 years of age. The committee also concurred with the approval and full pediatric assessment of D-QIV product with labeling down to age 6 months.

c) Bioresearch Monitoring Review

CBER Bioresearch Monitoring (BiMo) issued inspections for four foreign clinical investigator study site conducting Study D-QIV-004 in support of this sBLA. The BiMo inspections did not reveal significant problems that impact the data submitted in this application.

d) Clinical Serology Assays

To assess vaccine efficacy for various primary and secondary objectives, the RT-PCR assay and assays for antigenic characterization that were based on the haemagglutination inhibition (HI) and (b) (4) tests were used. Based on the results from the validation reports, the RT-PCR assay, (b) (4) haemagglutinin inhibition assay, and (b) (4) assay were determined to be fit for the intended use. For immunogenicity, the HI, (b) (4) assays were used. GSK used the HI assays for the influenza strains selected for the vaccination periods to assess the secondary immunogenicity objective. These HI assays have been

previously reviewed by CBER during the review of STN 125127/775, STN 125163/405, and STN 125127/513.

7. Safety

An analysis of safety and reactogenicity dataset was performed on the TVC, which includes a total of 7416 subjects from 6 months to 48 months of age who received at least one dose of D-QIV in the three studies and 6012 subjects received a control non-influenza vaccine (Table 1). Study D-QIV-004 and D-QIV-015 enrolled children ages 6 to 35 months of age and study D-QIV-009 enrolled children ages 17 to 48 months of age. In general for the 3 studies, the demographic characteristics of subjects in the TVC were comparable, with respect to mean age and gender distribution, between the study groups. The mean age at vaccination ranged between 19.7 and 21.9 months (subjects were older in study D-QIV-009 [32.5 to 33.2 months] as this was an extension to study D-QIV-004). Overall, 51.2% to 58.1% of the subjects were male. In studies D-QIV-009 and D-QIV-015, most of the subjects were of Caucasian origin (70.6% to 97.9%) whereas in study D-QIV-004, geographic ancestry of the subjects in the D-QIV group was distributed between Asian - south east Asian heritage (27.7%), White - Caucasian/European heritage (24.5% to 24.7%), Asian - central/south Asian heritage (17.5% to 17.7%) or other (27.3%).

The safety and reactogenicity evaluation in study D-QIV-004 included collection of local and systemic solicited adverse events (AEs) captured via diary card for 7 days post vaccination; unsolicited adverse events in the 28 days post-vaccination and serious adverse events (SAEs), potentially immune mediated diseases (pIMDs), medically attended AEs (MAEs), and deaths, for the 180-day study duration. SAEs, MAEs, and pIMDs were assessed at either day 28 (primed subjects) or days 28 and 56 (unprimed subjects) as well as at study completion (study day 180). At least one AE (any solicited or unsolicited, local or general) was reported within 7 days post-vaccination for 51.8% and 53.8% of subjects in the D-QIV and control groups, respectively. At least one grade 3 AE was reported for 6% and 6.2% of subjects in the D-QIV and control groups, respectively. Injection site pain was the most frequently reported solicited local AE (22.9% and 23.3% of subjects in the D-QIV and control groups, respectively). Grade 3 injection site pain was reported for 0.7% and 0.8% of subjects overall in the D-QIV and control groups respectively. After Dose 1, the incidence of injection site pain was 17.2% and 17.8% of subjects in the D-QIV and control groups, respectively. After Dose 2, the incidence of injection site pain was 14% and 14.2% of subjects in the D-QIV and control groups, respectively. Redness at the injection site after Dose 1 was reported for 13.1% and 14.1% of subjects in the D-QIV and control groups, respectively. There were no reports of Grade 3 redness in either group. Swelling at the injection site after Dose 1 was reported in 7.9% and 8.8% of subjects in the D-QIV and control groups, respectively. There was one report of Grade 3 swelling in the D-QIV group and none in the control group.

Overall, the most frequently reported solicited general AE was irritability/fussiness (23.4% and 24.2% of subjects in the D-QIV and control groups), followed by loss of appetite (20.8% and 21.8% subjects in the D-QIV and control groups), and drowsiness (17.3% and 19.1% subjects in the D-QIV and control groups). Grade 3 irritability/fussiness was reported for 0.7

and 1.1% of subjects in the D-QIV and control groups. Grade 3 loss of appetite was reported for 1.9% and 1.6% of subjects in the D-QIV and control groups. Grade 3 drowsiness was reported for 1% and 1.2% of subjects in the D-QIV and control groups (Table 4).

The most frequently reported solicited grade 3 general AE related to vaccination within 7 post-vaccination was fever (> 39^0C), reported for 1.3% and 1.4% of subjects in the D-QIV and control groups. After Dose 1, the incidence of irritability/fussiness was 16.2% and 17.5% of subjects in the D-QIV and control groups. After Dose 2, the incidence of irritability/fussiness was 13.5% of subjects in both the D-QIV and control groups.

Table 4: Study D-QIV-004. Percentage of subjects experiencing solicited local and systemic adverse events occurring within 7 Days of vaccination with Dose 1 (Total Vaccinated Cohort)

Subjects experiencing at least one local adverse event by maximum intensity	**D-QIV N[1]=5899 n[2] (%)**	**Control N=5896 n (%)**
Pain: Total	1015 (17.2)	1047 (17.8)
Grade 2[3] or 3[4]	190 (3.2)	190 (3.2)
Grade 3	23 (0.4)	30 (0.5)
Medical Advice	2 (0)	2 (0)
Redness: Total	775 (13.1)	831 (14.1)
> 20 mm	10 (0.2)	12 (0.2)
> 50 mm	1 (0)	0 (0)
Medical Advice	3 (0.1)	3 (0.1)
Swelling: Total	467 (7.9)	518 (8.8)
> 20 mm	26 (0.4)	19 (0.3)
> 50 mm	0 (0)	0 (0)
Medical Advice	2 (0)	3 (0.1)
Subjects experiencing at least one general adverse event by maximum intensity		
Drowsiness: Total	739 (12.5)	829 (14.1)
Grade 2 or 3[5]	177 (3)	206 (3.5)
Grade 3	39 (0.7)	59 (0.9)
Medical Advice	21 (0.4)	32 (0.5)
Irritability/Fussiness: Total	955 (16.2)	1029 (17.5)
Grade 2 or 3[6]	249 (4.2)	292 (5)
Grade 3	42 (0.7)	62 (1.1)
Medical Advice	38 (0.6)	44 (0.7)
Loss of Appetite: Total	847 (14.4)	872 (14.8)
Grade 2 or 3[7]	227 (3.8)	254 (4.3)
Grade 3	68 (1.2)	60 (1)
Medical Advice	47 (0.8)	39 (0.7)
Fever: Total	390 (6.6)	438 (7.4)
≥38^{0}C	372 (6.3)	425 (7.2)
>38.5^{0}C	160 (2.7)	194 (3.3)
>39^{0}C	78 (1.3)	76 (1.3)
>39.5^{0}C	29 (0.5)	36 (0.6)
>40^{0}C	3 (0.1)	8 (0.1)
Medical Advice	85 (1.4)	106 (1.8)

Source: Tables 74 and 75 of the clinical study report for FLU D-QIV-004 submitted to BLA 125127/834
[1]N: total number of subjects
[2]n: number of subjects per group
[3]Grade 2: cries/protests on touch

[4]Grade 3: cries when limb is moved/spontaneously painful
[5]Grade 2: interferes with normal activity, Grade 3: prevents normal activity
[6]Grade 2: crying more than usual/interferes with normal activity, Grade 3: Crying that cannot be comforted/prevents normal activity
[7]Grade 2: eating less than usual/interferes with normal activity, Grade 3: not eating at all.

During the 28 day post-vaccination period, at least one unsolicited AE was reported for 44% and 44.6% of subjects in the D-QIV and control groups, respectively (Table 5). Grade 3 unsolicited AEs were reported for 2.7% and 2.5% of subjects in the D-QIV and control groups. Nasopharyngitis (14.5% and 15.7% of subjects in the D-QIV and control groups, respectively) and upper respiratory infection (8.7% and 8.6% of subjects in the D-QIV and control groups, respectively) were the most frequently reported unsolicited AEs.

Table 5: Unsolicited adverse events in study D-QIV-004

	Group		
	D-QIV N=6006	**Control N=6012**	**Total N=12018**
Unsolicited adverse events	2640 (44.0%)	2679 (44.6%)	5319 (44.3%)
Grade 3 Unsolicited adverse events	160 (2.7%)	149 (2.5%)	309 (2.6%)
Unsolicited adverse events with causal relationship to vaccination	106 (1.8%)	116 (1.9%)	222 (1.8%)
Grade 3 Unsolicited adverse events with causal relationship to vaccination	7 (0.1%)	3 (0.0%)	10 (0.1%)

Source: Table 9.33 page 1560 of the clinical study report for FLU D-QIV-004 submitted to BLA 125127/834

At least one unsolicited AE with a medically attended visit (MAV) during the entire study period was reported for 64.7% and 66.3% of subjects in the D-QIV and control groups, respectively (Table 6). The most frequently reported unsolicited AEs with MAV were nasopharyngitis (29.0% and 30.0% of subjects in the D-QIV and Control groups, respectively). Grade 3 unsolicited AEs with MAV during the entire study were reported for 3.3% (D-QIV) and 3.5% (Control) of subjects.

Table 6: Medically attended events in study D-QIV-004

	Group		
	D-QIV N=6006	**Control N=6012**	**Total N=12018**
Unsolicited adverse events with medically attended events	3885 (64.7%)	3988 (66.3%)	7873 (65.5%)
Grade 3 Unsolicited adverse events with medically attended events	200 (3.3%)	211 (3.5%)	411 (3.4%)
Unsolicited adverse events with causal relationship to vaccination with medically attended events	57 (0.9%)	58 (1.0%)	115 (1.0%)
Grade 3 Unsolicited adverse events with causal relationship to vaccination with medically attended events	4 (0.1%)	2 (0.0%)	6 (0.0%)

Source: Table 9.35 of the clinical study report for FLU D-QIV-004 submitted to BLA 125127/834

Four subjects experienced a total of 6 SAEs associated with a fatal outcome. One subject was in the D-QIV group and the other 3 were in the control group. None of the SAEs with fatal outcome were attributed to the study vaccine. In the D-QIV, a 20-months old male child died due to drowning 23 days after receiving the first dose of D-QIV. In the control group, two subjects died due to drowning. One subject in the control group died from complications of bronchitis, pneumonia, and pleural effusion 51 days after the second dose of control vaccine.

In the D-QIV group, 217 out of 6006 subjects reported at least one unsolicited SAE (3.6%). Of those subjects, 6 were identified to have SAE caused by vaccination: immune thrombocytopenic purpura, hypersensitivity, nephrotic syndrome, apnea, and 2 facial paralysis febrile convulsion cases. In the control group, 201 out of 6012 subjects reported at least one unsolicited SAE (3.3%). Of those subjects, 2 were identified to have SAE caused by vaccination (febrile convulsion and seizure anoxic).

Potential immune-mediated diseases that included autoimmune diseases and other inflammatory and/or neurologic disorders were of special interest. A total of 5 subjects experienced one pIMD (immune thrombocytopenic purpura, coeliac disease, facial paralysis (2)), and 1 subject experienced 3 pIMDs (nephrotic syndrome, anaphylactic shock, and venous thrombosis) in D-QIV group, and none in the control group. Despite imbalance in the number of pIMDs between the control and D-QIV group, and the very small absolute number of pIMD cases in the D-QIV group (0.08% of study participants), the occurrence of these pIMDs do not represent a safety signal

For the D-QIV-009 study, during the 28-day follow-up post Dose 1, at least one unsolicited AE was reported for 27.4% and 28.8% of subjects in the vaccine-primed and vaccine-unprimed groups, respectively. Grade 3 unsolicited AEs were reported for 2.5% and 3.1% of the subjects and unsolicited AE with a causal relationship to vaccination for 2.1% and 1.3% of the subjects in the vaccine-primed and vaccine-unprimed groups, respectively. At least one unsolicited AE with a MAV during the 28-day follow-up post Dose 1 was reported for 20.3% and 21.4% of the subjects and during the entire study period for 61.8% and 56.8% of the subjects in the vaccine-primed and vaccine-unprimed groups, respectively. Grade 3 unsolicited AE with a MAV was reported for 1.7% of the subjects in each group, during the 28-day follow-up post Dose 1 and for 2.1% and 3.5% of the vaccine-primed and vaccine-unprimed groups, respectively, during the entire study period. One unsolicited AE with a MAV assessed by the investigator as causally related to the vaccine (upper respiratory tract infection) was reported during the 28-day follow-up post Dose 1 for one subject in the vaccine-unprimed group. A total of 15 subjects (7 [2.9%] in the vaccine-primed group and 8 [3.5%] in the vaccine-unprimed group) reported 19 SAEs during the entire study period. No vaccine-related SAEs were reported during the study. No pIMDs were reported during the entire study period.

For the D-QIV-015 study , pain was reported for 14.9% and 16.4% for subjects (6 through 35 months of age), in the D-QIV IP and the D-QIV LP groups respectively, during the 7-day follow-up period after dose 1. Only 1 subject (0.2%) in the D-QIV IP group and 2 subjects (0.4%) in the D-QIV LP group reported pain grade 3 after the first dose. Redness was reported for 19% and for 18.3% of the subjects in the D-QIV IP and the D-QIV LP groups respectively

and swelling was reported for 7.1% and for 8.9% of the subjects in the D-QIV IP and the D-QIV LP groups respectively. No grade 3 redness or swelling was reported in any of the treatment groups after dose 1 or dose 2. During the 7-day follow-up period, irritability/fussiness was the most frequently reported solicited general AE, reported for 26.8% of subjects in the D-QIV IP group and 20.4 % of subjects in the D-QIV LP group. The incidence of solicited local AEs and general AEs did not increase after the second dose. The incidence of fever ≥38°C (100.4°F) post dose 1 was 8.4% (39/462) and 8.9% (42/470) in the D-QIV IP and D-QIV LP groups respectively. The calculated RR for D-QIV IP over D-QIV LP for this endpoint was 0.94 (0.59; 1.50). Fever >39 °C (102.2 °F) was reported for 8 subjects (1.7%) in the D-QIV IP group and for 5 subjects (1.1%) in the D-QIV LP group. The calculated RR for D-QIV IP over D-QIV LP was 4.08 (0.40; 200.69). The incidence of olfactory refernce syndrome like symptoms was low and similar in both groups. Cough was the most frequently reported ORS like symptoms during the 3-day post vaccination period post Dose 1, 10.2% for D-QIV IP vs 10.6% for D-QIV LP. Post Dose 2, Cough related to vaccination was reported for 3.5% of subjects and 2.8% of subjects in the D-QIV IP and D-QIV LP groups respectively.

During the 28-day post-vaccination follow-up period, at least one unsolicited symptom was reported for 52.1% of subjects in the D-QIV IP group and 55.3% of subjects in the D-QIV LP group. Upper respiratory tract infection was the most frequent reported unsolicited AEs, reported by 13.3% of subjects in the D-QIV IP group and 15.4% of subjects in the D-QIV LP group. This was followed by bronchitis, reported for 8.6% of subjects in the D-QIV IP group and 12.2% of subjects in the D-QIV LP group.

During the entire study period, at least one unsolicited MAE was reported for 50.4% of subjects in the D-QIV IP group and for 53.2% of subjects in the D-QIV LP group. At least one grade 3 MAE was reported by 7.5% of subjects in the D-QIV IP group and 6.1% of subjects in the D-QIV LP group. Two subjects in the D-QIV IP group reported each one MAE assessed as causally related (vomiting and bronchitis). Bronchitis, reported by one subject in the D-QIV IP group was the only grade 3 MAE with causal relationship to vaccination. Seven subjects (1.5%) in the D-QIV IP group and 11 subjects (2.3%) in the D-QIV LP group reported at least one SAE during the entire study period. All the SAEs were resolved during the study period. The febrile seizure occurred 31 days after study vaccination and concomitantly with an adenovirus infection and was assessed as not related to the study vaccination.

Serious and other significant adverse events:

SAEs were generally balanced between the treatment groups in the 3 studies submitted. In the primary study D-QIV 004, at least one SAE was reported for 3.6% and 3.3% of subjects in the D-QIV and control groups, respectively. In supportive study D-QIV 009, at least one SAE was reported for 2.9% and 3.5% of subjects in the vaccine-primed and the vaccine-unprimed groups, respectively. In supportive study D-QIV 015, at least one SAE was reported for 1.5% and 2.3% of subjects in the D-QIV-IP and D-QIV-LP groups, respectively.

In study D-QIV-004, a total of 44 subjects experienced febrile convulsion over the entire study duration (21 subjects in the D-QIV group and 23 subjects in the Control group). Non-serious AEs of febrile convulsion were reported in 8 subjects in the D-QIV group and 8 subjects in the control group. All cases (serious and non-serious) of febrile convulsion resolved. Within 28 days after vaccination, febrile convulsions were reported by 8 subjects in the D-QIV group (6 SAEs) and 7 subjects in the control group (5 SAEs). Two subjects in the D-QIV group and 1 subject in the control group reported febrile convulsions with possible causal relationship to vaccination according to the Investigator as described below:

- Two days after dose 1 of D-QIV, a 26 month old child developed febrile convulsions with rhinitis and red throat. The subject had history of 2 prior episodes of febrile convulsion before study enrollment associated common colds.

- Ten days after dose 1 of D-QIV, a 22 month child developed febrile convulsion with upper respiratory tract infection symptoms.

In study D-QIV-009, one febrile convulsion was reported 100 days post-vaccination in the primed group and in study D-QIV-015, one febrile convulsion was reported 31 days post-vaccination in the D-QIV-LP group. Both febrile convulsions were resolved without sequalae and neither of which were considered related to the study vaccine.

Overall FLU D-QIV was well tolerated in individuals 6-35 months and no safety signals were observed in these three studies. Furthermore, analysis of safety data does not raise any safety concerns for use of this vaccine in individuals 6-35 months of age.

8. Advisory Committee Meeting

This submission was not discussed at a VRBPAC meeting because review of this submission did not identify concerns or issues which would have benefited from an advisory committee discussion.

9. Other Relevant Regulatory Issues

None

10. Labeling

The text “moderate to severe or of any severity” in the context of “Efficacy of FLUARIX QUADRIVALENT was assessed for the prevention of reverse transcriptase polymerase chain reaction (RT-PCR)-confirmed influenza°A and/or B°disease due to any seasonal influenza strain, compared with non-influenza control vaccines” was removed at multiple places in the proposed Package Insert including the Table 8. This was one of the key proposals by GSK to be included in the Package Insert. In the past communications (our written responses and teleconference minutes from April 28, 2011, May 31, 2011, June 1, 2011 [Type-A meeting discussion], September 17, 2012, December 18, 2012, December 19, 2012, and March 13,

2013) as well during the current labeling negotiations, CBER had maintained that the primary endpoint of the pivotal efficacy study; D-QIV-004 should be the prevention of culture-confirmed influenza due to influenza strains contained in the vaccine. GSK had proposed the composite endpoint of moderate to severe influenza but CBER did not agree that the component endpoints constituted moderate or severe disease due to the inconsistencies in diagnosis of Acute Otitis Media and Lower Respiratory Infection, and the wide variation in severity of the adverse outcomes (e.g., fever >39^{o}C) in the composite. Therefore CBER did not allow the use of the term in the Package Insert.

Negotiations and CBER recommendations resulted in the following changes to the current label:

1) Description of Adverse Reactions (at multiple places throughout the Package Insert including contents described in tables):
   - "Injection Site" was changed to "Solicited local"
   - "Events" were changed to "Reactions" – to indicate the causal association of adverse reactions with the vaccination.
   - Percentage of children (6-35 months) who experienced redness (13%) was misindicated as those who experienced swelling. This error was corrected.
2) In Section 2.2, Administrative Instructions, addition of "if muscle mass is adequate" at line 20 to provide clear instructions to the physicians.
3) In Section 6.1, Clinical Trial Experience,
   - addition of text to describe the dosing and manufacturing information for vaccines used in the control group of Trial 7 (NCT01439360). These information was also included in the footnote of Table 7.
   - mean age: 22 months was added in line 124.
   - "Frequencies" was changed to "Incidences" to better describe the listing of adverse reactions.
   - Table 3: Non-Influenza Active comparator was added in the title of the column 2 as well as the table footnote.
   - Two sentences were deleted from the first paragraph of page 7, because the descriptions provided were inaccurate.
4) In Section 6.2, Postmarketing Experience, "This list includes serious events or events which have causal connection to FLUARIX" was deleted as these events were reported voluntarily.
5) In Section 8.4, Pediatric Use, "Immunogenicity" was replaced by "Effectiveness" since the primary endpoints were based on efficacy.
6) In Section 11, Description, influenza strains were updated for 2017-2018 influenza seasons.
7) In Section 14.1, Efficacy Against Influenza, the demographics of the population was included for the Trial 7 description (page 17 line 418).

8) Table 8 was modified to include the strains information for the D-QIV used in different seasons as text, and deleted from the Table. Details describing vaccine efficacy against moderate to severe influenza, RT-PCR confirmed Influenza associated with Lower Respiratory Tract Infection (LRI) and Acute Otitis Media (AOM) outcomes, were removed. These details were represented in text format below Table 8.RT-PCR confirmed Influenza cases associated with adverse outcomes and the incidence of the specified adverse outcomes are presented in Table 9.
9) Description of Attack Rates and vaccine efficacy for RT-PCR confirmed Moderate to Severe Disease by Influenza A Subtype and Influenza B Lineage in Children Aged 6 through 35 months was removed from Table 10.

The revised D-QIV package insert (PI) with data from this supplement in support of the inclusion of children 6-35 months of age were reviewed by relevant members of the review committee, including clinical, statistical, and APLB reviewers. The revised D-QIV PI approved with this supplement incorporates information from D-QIV-004 study into the "Clinical Studies" sections.

The "Use In Specific Populations" section of the PIs was also revised to comply with the Requirements for Pregnancy and Lactation Labeling, referred to as the "Pregnancy and Lactation Labeling Rule" (PLLR rule), published by FDA in December 2014.

Minor changes to improve clarity and consistency were made throughout the PI. The committee concurs that the PI submitted on January 3, 2018, is acceptable. Proposed carton label, submitted on September 12, 2017, was reviewed and found to be acceptable. The container label was not submitted in this supplement, as there were no changes in the container label that was approved uner STN 125127/843 (2017/2018 annual strain change supplement).

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

It is the consensus of the review committee to recommend approval of this application to extend the age indication for D-QIV for active immunization of children ages 6 months and above against influenza disease caused by influenza subtypes A and type B contained in the vaccine.

b) Risk/ Benefit Assessment

Data submitted to the sBLA establish a substantial likelihood of benefit for children ages ≥ 6 to < 36 months who receive D-QIV for prevention of laboratory-confirmed influenza caused by any influenza viral type/subtype included in the vaccine. The risks of vaccination with D-QIV in children ages ≥ 6 to < 36 months have been found to be minimal. Thus, the overall risk-benefit profile of this product is determined to be favorable.

c) Recommendation for Postmarketing Risk Management Activities
No safety issues were identified that would have warranted a Risk Evaluation and Mitigation Strategy (REMS) or a new Postmarketing Requirement (PMR).

d) Recommendation for Postmarketing Activities
No changes to the submitted pharmacovigilance plan for D-QIV are recommended based on the information contained in this application.

e) Pharmacovigilance plan
The pharmacovigilance plan proposed by GSK [Fluarix Quadrivalent (D-QIV) United States Pharmacovigilance Plan, Version 1: 10.0 data lock point 13 July 2016] appears adequate. Postmarketing adverse experiences should be reported to CBER in accordance with 21 CFR 600.80.

References:

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