Summary Basis of Regulatory Action

Date: November 18, 2016
From: Goutam Sen, Ph.D., Chair of the Review Committee
BLA/ STN#: 125163/405

Applicant Name: ID Biomedical Corp of Quebec dba GlaxoSmithKline's Biologicals

Date of Submission: January 27, 2016
PDUFA Goal Date: November 26, 2016

Proprietary Name: FluLaval®
Established Name: Influenza Vaccine

Indication: FluLaval 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 above.

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.**

Specific documentation used in developing the SBRA	**Reviewer Name**
Clinical Review	Sarah Browne, M.D., 10/13/2016
Statistical Review	Sang Ahnn, Ph.D., 10/13/2016
Bioresearch Monitoring Review	Dennis Cato., 9/21/2016
Labeling – APLB review	Sonny Saini., 9/30/2016
Product Review	Ewan Plant, Ph.D., 6/30/2016
Assay Review	Charles Cheung, Ph.D., 10/13/2016
Pharmacovigilance Review	Craig Zinderman, M.D., 10/18/2016

Cross referenced applications:

- IND 14466, Influenza Virus Quadrivalent Purified Hemagglutinin (2010/2011 A/A/B strains plus B Yamagata; embryonated hen's eggs; Flulaval process) Vaccine (FLU Q QIV)

- BLA 125163/253, To include a quadrivalent influenza virus vaccine formulation (FluLaval Quadrivalent) for the prevention of influenza disease in persons 3 years of age or older caused by influenza viruses contained in the vaccine.

- BLA 125163/254, To include use of FluLaval trivalent formulation in persons 3 years to 17 years of age for the prevention of influenza disease caused by influenza viruses contained in the vaccine.

1. Introduction

FluLaval Quadrivalent formulation 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 FluLaval 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) and 5mL multi-dose vial (10 doses of 0.5mL) containing thimerosal, a mercury derivative added as a preservative (each 0.5 mL dose contains 25 mcg mercury). 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. FluLaval Quadrivalent formulation is also referred to as Q-QIV in this summary.

ID Biomedical Corp of Quebec dba GlaxoSmithKline's Biologicals (referred as GSK throughout this document) submitted this supplemental Biologics Licensing Application (sBLA) on January 27, 2016, to extend the age indication for prevention of influenza disease in children 6 to 35 months based on safety and immunogenicity data from a Phase 3 clinical study, FLU Q-QIV-022. In this study, safety and immunogenicity of Q-QIV were compared to Sanofi Pasteur's quadrivalent influenza vaccine Fluzone Quadrivalent (also referred to as F-QIV in this summary) in children 6 to 35 months of age. Q-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 a 0.25 mL volume of F-QIV containing 30 µg of HA (7.5 µg of each of the four vaccine strains), which is the U.S. licensed formulation of F-QIV for this age group. Revised labeling for both FluLaval trivalent and quadrivalent formulations were 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].

FluLaval was licensed in the U.S. on October 5, 2006, 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 FluLaval in clinical studies in adults 18 through 49 years of age. Since products approved under the accelerated approval regulations (21 CFR 601.41) require further studies that are adequate and well controlled to verify and describe clinical benefit, a clinical endpoint efficacy study (IDB-707-106; NCT00216242) was conducted in adults 18 through 49 years of age. In this study, the efficacy against culture-confirmed, antigenically matched strains was 46.3%, with a lower limit (LL) of the one-sided 97.5% confidence interval (CI) of 9.8%. As the pre-specified success criterion for the lower limit of the CI was ≥35%, vaccine efficacy was not demonstrated according to the pre-defined criteria, regular approval was not granted. It was noted however, that the 1.2% attack rate in the placebo group for culture-confirmed, antigenically matched strains was lower than expected, contributing to a wide confidence interval for the estimate of vaccine efficacy.

A clarification letter was issued to GSK on June 1, 2011, containing PREA-related PMRs for: 1) a non-inferiority study comparing FluLaval to Fluzone in children 3 to 17 years of age; and 2) a clinical endpoint efficacy study of Q-QIV in children 3 to 8 years of age.

After discussions with CBER, GSK conducted a second confirmatory study. This study was a randomized, controlled, observer-blind, clinical endpoint study in 5200 children 3 through 8 years of age demonstrating absolute efficacy of Q-QIV for prevention of reverse-transcriptase polymerase chain reaction (RT-PCR)-confirmed influenza A and/or B disease presenting as influenza like illness (ILI) caused by community acquired influenza strains (reviewed under STN: 125163/253). This study would also confirm the clinical benefit of FluLaval trivalent formulation. The study estimated an absolute vaccine efficacy of 55.4% (LL of 95% CI was 39%), which satisfied the pre-specified criterion for demonstration of effectiveness (LL 95% CI > 30%). Concurrently, because the original approval of FluLaval was based on evaluation of adults, GSK conducted a PREA-required safety and immunogenicity study and demonstrated safety and immunologic noninferiority of FluLaval trivalent vaccine with Fluzone trivalent vaccine as a comparator, in children ages ≥3 to < 18 years (reviewed under STN: 125163/254). Together these studies supported traditional approval of both FluLaval trivalent and Q-QIV vaccines for persons ages ≥ 3 years of age. Of note, the manufacturing process of both the FluLaval trivalent and Q-QIV formulations are the same. The Q-QIV formulation was approved on August 15, 2013 for use in persons 3 years of age and older.

A PREA postmarketing requirement was included in the approval letters of STN 125163/253 and STN 125163/254 to conduct a pediatric study to evaluate the safety and immunogenicity of Q-QIV in children 6 to 35 months of age. Agreement was reached between CBER and GSK at a Type C meeting held on March 18, 2014, about the sample size and safety and immunogenicity endpoints for the primary supportive study, FLU Q-QIV-022.

3. Chemistry Manufacturing and Controls (CMC)

No manufacturing changes were proposed in this supplement, since this product is currently licensed and no formulation changes were made.

4. Nonclinical Pharmacology/Toxicology

No 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

a) Clinical Program

All studies were conducted under US IND 14466 with the exception of study FLU Q-QIV-013 for which the clinical study report was provided after study completion. The primary immunogenicity and safety data to support use of FluLaval (both Q-QIV and Trivalent formulations) in the requested age indication was collected from one Phase 3 clinical trial conducted in children ages $\geq$ 6 to < 36 months, study FLU Q-QIV-022. However, three additional studies, FLU Q-QIV-021, FLU Q-QIV-013, and FLU Q-QIV-003 are described briefly in this submission (summarized in Table-1). The data from these three 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), but were not included in the integrated summary of immunogenicity because:

- they were small descriptive studies that did not evaluate the same primary immunogenicity endpoints as FLU Q-QIV-022;
- studies FLU-Q-QIV-021 and FLU-Q-QIV-013 used different active comparators from study FLU Q-QIV-022, both of which were trivalent formulations (Fluzone and Fluarix); and
- the sub-study of FLU-Q-QIV-003 which enrolled children ages ≥6 to < 36 months was single-arm and open-labeled.

Table 1. Summary of Primary Study FLU Q-QIV-022 and 3 Supportive Studies Evaluating FluLaval-QIV in Healthy Children Ages 6 through 35 Months.

Study number (NCT number)	Countries (number of sites)	Study design[1]	Treatment arms (N[2])
FLU Q-QIV-022 (NCT02242643)	Mexico (2) US (67)	Phase 3, double-blind, randomized, active-controlled	FluLaval-QIV[3] (1207) Fluzone-QIV (1217)
FLU Q-QIV-021 (NCT01974895)	US (12)	Phase 2, observer-blind, randomized, active-controlled study	FluLaval-QIV (158) Fluzone (156)
FLU Q-QIV-013 (NCT01711736)	Canada (6), Dominican Republic (1), Honduras (1)	Phase 3, double-blind, randomized, active-controlled	FluLaval-QIV (299) Fluarix (302)
FLU Q-QIV-003 (NCT01198756)	Canada (9), Mexico (2), Spain (4), Taiwan (2), US (16)	Open label[7]	FluLaval-QIV (301)

Source: Adapted from BLA 125163/405.0, 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 FLU Q-QIV-022 was a Phase 3, randomized, controlled, multi-center, observer-blind study conducted in the U.S. and Mexico that enrolled 2430 subjects, to compare the safety and immunogenicity of Q-QIV with F-QIV in children ages ≥6 to < 36 months. The primary objective was to demonstrate the immunogenic non-inferiority of Q-QIV versus F-QIV (in terms of geometric mean titers [GMTs] and SCRs) approximately 28 days after completion of dosing (Day 28 and Day 56 for vaccine primed and vaccine-unprimed subjects).

Of the 2430 subjects enrolled, 2424 were vaccinated [Total Vaccinated Cohort (TVC)], among them 1207 received Q-QIV and 1217 received F-QIV achieving a 1:1 ratio. The study was conducted at 67 sites in the U.S. enrolling 2232 (92.1%) subjects, and 2 sites in Mexico enrolling 192 (7.9%) subjects. The demographic characteristics were similar between the two treatment groups. A total of 1002 subjects in TVC cohort (41.3%) were 6-17 months of age.

Primed (those who had received influenza vaccine previously) subjects received a single IM dose of study vaccine whereas unprimed (those who had not received influenza vaccine previously) subjects received 2 doses 28 days apart. Vaccines used in the study were: 2014-15 season's WHO and VRBPAC recommended Northern hemisphere Q-QIV (0.5 mL) and F-QIV (0.25 mL) [A/Christchurch/16/2010 (H1N1); A/Texas/50/2012 (H3N2); B/Massachusetts/02/2012 (Yamagata lineage); B/Brisbane/60/2008 (Victoria lineage)]. All subjects had blood drawn for evaluation of HAI titers at Day 0 (baseline) and at 28 days after completion of the vaccination regimen (Day 28 for primed subjects or Day 56 for unprimed subjects).

The primary endpoints of immunologic noninferiority for all four vaccine strains were Q-QIV compared to F-QIV GMT ratios and seroconversion rate differences. In the ATP Cohort for immunogenicity, non-inferior immunogenicity success criteria of Q-QIV compared to F-QIV

were the upper limit of the 2-sided 95% CI for the GMT ratio (F-QIV/Q-QIV) of < 1.5, and the upper limit of the 2-sided 95% CI for the difference in SCRs (F-QIV – Q-QIV) of <10%, for each of the 4 strains.

Immunogenicity results on TVC were similar to the immunogenicity results on the ATP Cohort. Among the subjects in this study (6-35 months of age), Q-QIV was immunogenically non-inferior to F-QIV in terms of GMT ratio and SCR difference for all four strains contained in the vaccine, as shown in Tables 2 and 3. The pre-specified immunogenicity success criteria were met for all primary and secondary endpoints. The 95% CI was below one for GMT ratios and below zero for SCR differences favoring Q-QIV for all strains (the range of ULs of the difference in SCRs for F-QIV minus Q-QIV was -12.02% to -2.27% for the 4 strains); and 95% CIs did not overlap for both influenza B strains in the secondary descriptive endpoints. This could be explained by the fact that Q-QIV contains twice the antigen load as F-QIV.

Table 2. Non-Inferiority[1] Comparison of Geometric Mean Hemagglutinin Inhibition Antibody Titers Against Influenza Vaccine Strains 28 Days after Last Vaccination[2] for Study FLU Q-QIV-022 (ATP[3] Cohort for Immunogenicity)

Strain	Fluzone-QIV[4] Adjusted GMT[5] N[6] = 972	FluLaval-QIV Adjusted GMT N = 980	Ratio Fluzone-QIV: FluLaval-QIV (95% CI[7])
A/California/7/2009 (H1N1)	85.1	99.6	0.85 (0.77, 0.95)
A/Texas/50/2012 (H3N2)	84.6	99.8	0.85 (0.77, 0.94)
B/Massachusetts/2/2012 (Yamagata)	167.3	258	0.65 (0.59, 0.71)
B/Brisbane/60/2008 (Victoria)	33.7	54.5	0.62 (0.56, 0.69)

Source: Adapted from BLA125163/405.0: Clinical Study Report Table 22
[1]Non-inferiority (GMTs): upper limit of 95%CI for ratio of Fluzone-QIV: FluLaval-QIV ≤ 1.5
[2]Study Day 28 for primed subjects and Day 56 for unprimed subjects
[3]ATP: according to protocol; [4]QIV: quadrivalent
[5]Adjusted GMT: geometric mean titers, adjusted for baseline titer
[6]N: number of subjects; [7]CI: confidence interval

Table 3. Non-Inferiority[1] Comparison of Seroconversion Rates[2] for Influenza Vaccine Strains 28 Days after Last Vaccination[3] for Study FLU Q-QIV-022 (ATP[4] Cohort for Immunogenicity)

Strain	Fluzone-QIV[5] SCR N[6] = 972 N[7] (%)	FluLaval-QIV SCR N = 980 n (%)	SCR difference Fluzone-QIV- FluLaval-QIV (95% CI[8])
A/California/7/2009 (H1N1)	660 (67.3)	716 (73.7)	-6.32 (-10.35, -2.27)
A/Texas/50/2012 (H3N2)	680 (69.4)	740 (76.1)	-6.74 (-10.68, -2.80)
B/Massachusetts/2/2012 (Yamagata)	475 (48.5)	631 (64.9)	-16.38 (-20.68, -12.02)
B/Brisbane/60/2008 (Victoria)	723 (73.8)	833 (85.5)	-11.75 (-15.28, -8.21)

Source: Adapted from BLA125163/405.0: Clinical Study Report Table 22
[1]Non-inferiority (SCRs): lower bound of 95%CI for ratio of Fluzone-QIV minus FluLaval-QIV ≤ 10%
[2]SCR: Seroconversion rate; defined as a prevaccination HI titer <10 and postvaccination HI titer ≥ 40, or at least a 4-fold increase in HI titer from prevaccination titer ≥ 10
[3]Study Day 28 for primed subjects and Day 56 for unprimed subjects
[4]ATP: according to protocol
[5]QIV: quadrivalent
[6]N: total number of subjects
[7]n: number of subjects with specified characteristic
[8]CI: confidence interval

The secondary immunogenicity endpoint was to assess the HI response elicited by Q-QIV in children 6-35 months of age 28 days after the last vaccination regimen. Success criteria for SCR was defined as a prevaccination HI titer <10 and postvaccination HI titer ≥ 40, or at least a 4-fold increase in HI titer from prevaccination titer ≥ 10, (LL of the two-sided 95% CI for SCR should be ≥40% for each strain). Success criteria for SPR criteria was defined as the percentage of vaccinees with a serum HI titer ≥ 40 indicating protection in at least 50% of vaccines (LL of the two-sided 95% CI for SCR should be ≥70% for each strain). The three vaccine strains met success criteria for both SCR and SPR, whereas the B Victoria strain met only SCR success criteria. For Q-QIV, the range of LLs for SCR was 61.8% to 83.2% for the 4 strains; the range of LL for SPR was 63.0% for B/Victoria strain and 77.8% to 95.8% for the other 3 strains. The licensed comparator vaccine in the study, F-QIV, also met the SCR and SPR criteria for all strains except B Victoria. Similar to Q-QIV, F-QIV met the SCR for the B Vicotria strain, but did not meet SPR success criteria (LL of the 2-sided 95% CI for the SPR was 46.7%). In general, rates were lower in the younger cohort (6 to 17 months) versus the older cohort (18 to 35 months) and for unprimed versus primed subjects. These differences were observed in both treatment arms and followed the same immunogenicity trends.

Subgroup Analyses

The demographic profile of the treatment groups in each study was comparable with respect to mean age (at vaccination with dose 1), gender, and geographic ancestry/ethnicity distribution. There was an approximately equal distribution of males and females and most children were of White-Caucasian/European heritage, except in the FLU Q-QIV-013 study, where the majority were in the "Other" category (i.e., American Hispanic or Latino ethnicity). Post hoc

subgroup analyses did not demonstrate any clinically significant differences with respect to immunogenicity and safety by age, sex, ethnicity, and country.

b) Pediatrics

FluLaval (trivalent formulation) and Q-QIV are currently approved for use in persons ages 3 years and older. The approval letters for STN: 125163/253 and STN: 125163/254, established Postmarketing Requirements that required GSK to conduct a PREA clinical study to evaluate the safety and immunogenicity of Q-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. During the review of STN: 125163/253 and 125163/254, GSK received a waiver for infants <6 months of age based on the reasoning that FluLaval and Q-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 concurred with the approval and full pediatric assessment of both FluLaval and Q-QIV products with labeling down to age 6 months.

c) Bioresearch Monitoring Review

CBER Bioresearch Monitoring (BiMo) issued inspections for one domestic and one foreign clinical investigator study site conducting Study FLU Q-QIV-022 in support of this sBLA. The BiMo inspections did not reveal significant problems that impact the data submitted in this marketing application.

d) Clinical Serology Assays

To support immunogenicity evaluation, HAI assays were used in all the four clinical studies, supporting this supplement. GSK has submitted 6 validation reports (4 from Dresden and 2 from Laval) of the HAI assays. The results demonstrated that the assays for A/Texas/50/2012 (Laval), B/Massachusetts/2/2012 (Laval), A/Texas/50/2012 (Dresden), and B/Massachusetts/2/2012 (Dresden) were acceptable for the intended use in this submission. The assays for A/Victoria/361/2011 and B/Hubei-Wujiagang/158/2009 used in Study FLU Q-QIV-013 passed the acceptance criterion for specificity, which was the only parameter validated.

7. Safety

An analysis of safety dataset was performed on the TVC, which includes a total of 1965 subjects from 6 months to 35 months of age who received at least one dose of Q-QIV in the four studies and 1675 subjects received a control vaccine (Table 1). The demographic profile of the treatment groups in each study was comparable with respect to mean age (at vaccination with dose 1), gender, and geographic ancestry/ethnicity distribution. There was an approximately equal distribution of males and females and most children were of White-

Caucasian/European heritage, except in the FLU Q-QIV-013 study, where the majority fell in the "Other" category (i.e., American Hispanic or Latino ethnicity).

The safety evaluation in study FLU Q-QIV-022 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, 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). Safety profile of Q-QIV appeared generally comparable to F-QIV. For both vaccines injection site pain was the most commonly reported local AE [44.0% (95% CI: 41.1, 46.9) in the Q-QIV group and 40.1% (95% CI: 37.3, 43.0) of subjects in the F-QIV group]. Grade 3 injection site pain was reported for 2.9% and 1.7% of subjects in the Q-QIV and F-QIV groups, respectively. Overall, irritability/fussiness was the most frequently reported solicited systemic AE [54.4% (95% CI: 51.4, 57.3) and 50.5% (95% CI: 47.6, 53.4) of subjects in the Q-QIV and F-QIV groups] followed by drowsiness [40.6% (95% CI: 37.8, 43.5) and 40.9% (95% CI: 38.0, 43.8)] of subjects, in the Q-QIV and F-QIV groups and loss of appetite [33.7% (95% CI: 31.0, 36.5) and 33.4% (95% CI: 30.7, 36.2) of subjects in the Q- QIV and F-QIV groups]. Grade 3 irritability/fussiness was reported for 5.3% and 3.9% of subjects, respectively. Grade 3 drowsiness was reported for 3.1% and 3.0% of subjects, respectively. Grade 3 loss of appetite was reported for 2.2% and 1.6% of subjects, respectively.

Rates of fever were similar across treatment arms. During the 7-day (Day 0-6) follow-up, fever (≥38°C) was reported for 7.9% (95% CI: 6.4, 9.6) and 7.5% (95% CI: 6.0, 9.1) of subjects in the Q-QIV and F-QIV groups, respectively. Grade 3 or higher fever (>39°C) was reported for 2.2% and 1.5% of subjects, in the Q-QIV and F-QIV groups, respectively. The relative risk of grade 3 or above fever (>39.0°C) for subjects in the Q-QIV group compared to the subjects in the F-QIV group, during a 2-day (48 hours) follow-up period was 1.49 (95% CI: 0.47, 5.09). Q-QIV contains twice the antigen load (60 µg; 15 µg of each of the four HA antigens) as F-QIV (30 µg; 7.5 µg of each of the four HA antigens) and therefor might be anticipated to be more reactogenic. The review team had questions of the fever data, as approximately 2% of temperature observations were recorded as ≤35°C. The applicant attributed this to "mishandling by the parents". Whether this was restricted to fever observations ≤35°C or affected all fever observations is not verifiable. However, no significant difference in the distribution of fever between the two arms was observed. There were more subjects in the Q-QIV group than in the F-QIV group with temperatures ≥ 39.5°C (15 versus 5 subjects) and ≥ 40°C (5 and 0 subjects). In the System Organ Class for nervous system disorders 9 febrile seizures occurred (5 subjects in the Q-QIV group and 4 subjects in F-QIV groups). One febrile seizure occurred within 7 days of vaccination in a subject who received Q-QIV (study day 4). The subject had been afebrile the day prior and had a temperature of > 40°C associated with wild type influenza infection on study day 5 at the time of the seizure. The remaining seizures occurred greater than one-month postvaccination (range 39-178 days), suggesting underlying etiologies other than vaccination. While the study was underpowered to detect statistical differences in rates of febrile seizures, no imbalances were noted between the treatment arms. There were no other major safety concerns raised by the review team.

In the studies FLU Q-QIV-021, FLU Q-QIV-013, and FLU Q-QIV-003, there were no imbalances observed in local or systemic reactogenicity through study day 7 or unsolicited AEs through study day 28. There were no imbalances in MAEs, or SAEs and there were no pIMDs or deaths reported during the 180 day study period.

Table 4. Solicited Systemic and Local AEs by Type and Maximum Severity Occurring within 7 Days of Vaccination with Dose 1 and Dose 2 combined for Study FLU Q-QIV-022 (Total Vaccinated Cohort)

Subjects experiencing at least one local AE[1] by maximum intensity	Fluzone-QIV N[2] = 1152 n[3] (%)	FluLaval-QIV N = 1159 n (%)
Drowsiness: Total	471 (40.9)	471 (40.6)
Drowsiness: Grade 2 or 3[4]	177 (15.4)	160 (13.8)
Drowsiness: Grade 3	34 (3.0)	36 (3.1)
Drowsiness: Medical advice	13 (1.1)	15 (1.3)
Fever: Total	178(15.5)	183 (15.8)
Fever: ≥ 38°C	86 (7.5)	91 (7.9)
Fever: ≥ 38.5°C	41 (3.6)	48 (4.1)
Fever: ≥ 39.0°C	17 (1.5)	25 (2.2)
Fever: ≥ 39.5°C	5 (0.4)	15 (1.3)
Fever: ≥ 40°C	0 (0)	5 (0.4)
Fever: Medical Advice	17 (1.5)	24 (2.1)
Irritability/Fussiness: Total	582 (50.5)	630 (54.4)
Irritability/Fussiness: Grade 2 or 3[5]	229 (19.9)	265 (22.9)
Irritability/Fussiness: Grade 3	45 (3.9)	61 (5.3)
Irritability/Fussiness: Medical advice	22 (1.9)	23 (2.0)
Loss of appetite: Total	385 (33.4)	391 (33.6)
Loss of appetite: Grade 2 or 3[6]	112 (9.7)	109 (9.4)
Loss of appetite: Grade 3	19 (1.6)	26 (2.2)
Loss of appetite: Medical advice	19 (1.6)	17 (1.5)
Pain: Total	462 (40.1)	509 (44.0)
Pain: Grade 2 or 3[7]	150 (13.0)	164 (14.2)
Pain: Grade 3	19 (1.7)	34 (2.9)
Pain: Medical advice	3 (0.3)	0 (0)

Source: Adapted from BLA125163/405.0: Summary of Clinical Study Report Tables 8 and 22
[1]AE: adverse event
[2]N: total number of subjects
[3]n: number of subjects per group
[4]Grade 2 drowsiness interferes with normal activity and Grade 3 prevents normal activity
[5]Grade 2 crying more than usual or interferes with normal activity and Grade 3 cannot be comforted
[6]Grade 2 eating less than usual or interferes with normal activity and Grade 3 not eating at all
[7]Grade 2: cries/protests on touch and Grade 3: cries when limb is moved/spontaneously painful

The sample size for the primary supportive study, FLU Q-QIV-022, was sufficient to adequately characterize local and systemic reactogenicity for Q-QIV as described above. Given that each study had different comparators (one with Fluzone-TIV, one with Fluarix-TIV and one single-arm and open-label), the integrated safety analysis is focusing on rare and serious event (deaths, SAEs, pIMDs) for supportive studies FLU Q-QIV-021, FLU Q-QIV-013, and FLU Q-QIV-003.

SAEs were generally balanced between treatment arms in these 3 studies with comparator arms. In the TVC, a total of 56 SAEs were reported on 43 subjects during the entire study period. In the primary study FLU Q-QIV-022, 29 SAEs were reported for 22 subjects (1.8%) in the Q-QIV group, and 28 SAEs were reported for 21 subjects (1.7%) in the F-QIV group. All SAEs in the Q-QIV group were reported as resolved with the exception of one case of Kawasaki's disease (93 days after receiving one dose of the vaccine, age at onset was 17 months) and one case of croup (age at onset; 19 months). All SAEs in the F-QIV group were also reported as resolved at the time of the report with the exception of 4 SAEs (B precursor type acute leukemia, failure to thrive, developmental delay and hemiplegia) reported in 3 subjects (developmental delay and hemiplegia occurred in the same subject, age at onset was 36 months).

Serious and other significant adverse events:

No deaths were reported across the four studies. Among the 4 studies, one subject was withdrawn subsequent to a non-serious adverse event (moderate fever) which was reported as resolved. This subject was enrolled in the study Q-QIV-003.

During the entire study period, 4 cases of pIMD were reported in 4 subjects across the 4 studies.

- Two cases of pIMD were reported in study Q-QIV-022. One pIMD was in the Q-QIV group (Kawasaki's disease which was also reported as an SAE) and the other in the F-QIV group (Erythema multiforme). Both were reported as recovered/resolved at the time of the study report.

- Two cases of pIMD were reported in study Q-QIV-013, but both cases in the comparator group. Both were reported as resolved at the time of the study report.

There were 13 reports of seizures s across the 4 studies, 11 of which occurred in the setting of fever. Nine of these events occurred in the primary study FLU Q-QIV-022 (5 subjects in the Q-QIV group and 4 subjects in the F-QIV group). One febrile seizure occurred on study day 0 in an 18-month old male who received Q-QIV in the study Q-QIV-013 and another febrile seizure occurred on study day 18 in a subject receiving Q-QIV in the single arm open label study, FLU Q-QIV-003. Two seizures were not fever-associated (one on study day 70 in a subject receiving Fluzone TIV and one on study day 0 in a subject receiving Q-QIV, again in study FLU Q-QIV-003). Overall, the other reported SAEs were reasonably attributed to etiologies other than vaccination and the nature of SAEs reported were consistent with events that might occur in the age range being studied, for example, respiratory infections, asthma, gastroenteritis, trauma.

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

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

- In Section 6.1, Clinical Trials Experience, CBER requested that the Applicant expand the safety tables 2 through 5, describing overall rates of local and systemic reactogenicity for each age range so that they specifically describe rates of grade 3 adverse reactions. CBER considered the severe reactions to be clinically important information for prescribers.

- In Section 6.2, Postmarketing Experience, the Applicant distinguished between safety reports occurring for FluLaval (trivalent) and Q-QIV. This resulted in only one event being reported for Q-QIV, in allergic reactions under the subheading *Immune System Disorders*. Because the formulation of these products is identical except for the one additional influenza B strain contained in the Quadrivalent formulation, CBER requested that adverse events be consolidated and reported together for both products based on the rationale that a similar safety profile would be anticipated given the similarity of the products.

The revised FluLaval Trivalent and Q-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 FluLaval Trivalent and Q-QIV PIs approved with this supplement incorporates information from FLU-Q-QIV-022 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 PIs submitted on November 16, 2016, are acceptable. Proposed carton/container labels were reviewed and found acceptable.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

It is the consensus of the review committee to approve this application to extend the age indication for Q-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 BLA supplement establish a substantial likelihood of benefit for children ages ≥ 6 to < 36 months who receive Q-QIV for prevention of laboratory-confirmed influenza caused by any influenza viral type/subtype included in the vaccine. The risks of vaccination with Q-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 Q-QIV are recommended based on the information contained in this application.

e) Pharmacovigilance plan
The pharmacovigilance plan proposed by GSK [FluLaval Quadrivalent (FLU Q-QIV) United States Pharmacovigilance Plan, Version 2: January 2016] appears adequate. Postmarketing adverse experiences should be reported to CBER in accordance with 21 CFR 600.80.

References:

1. Thompson W., Shay D., Weintraub E., Brammer L., Bridges C., Cox N., et al. Influenza-associated hospitalizations in the United States. JAMA 292:1333–1340, 2004.
2. Centers for Disease Control and Prevention (CDC) Influenza activity – United States, 2014–15 season and composition of the 2015–16 influenza vaccine. MMWR Morb Mortal Wkly Rep 64: 583–590, 2015.
3. Schanzer D, Langley J, Tam T. Hospitalization Attributable to Influenza and Other ViralRespiratory Illnesses in Canadian Children. *Pediatr Infect Dis J* 25:795-800, 2006.
4. CDC (Centers for Disease Control and Prevention). Influenza vaccination coverage among children aged 6-23 months--United States, 2005-06 influenza season. MMWR 56(37):959-63, 2007.
5. Poehling KA, Edwards KM, Weinberg GA, Szilagyi P et al, for the New Vaccine Surveillance Network. The under-recognized burden of influenza in young children.NEJM 355:31-40, 2006.