Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

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Subject: Safety and Utilization Review for the Pediatric Advisory Committee

Applicant: ID Biomedical Corporation of Quebec [Subsidiary of GlaxoSmithKline Biologicals (GSK)]

Product: FluLaval Quadrivalent (influenza vaccine)

STN: 125163/597

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

Meeting Date: Pediatric Advisory Committee Meeting, September 2020

Contents

1 INTRODUCTION

1.1 Objective

This memorandum for the Pediatric Advisory Committee (PAC) presents a comprehensive review of the postmarketing pediatric safety covering a period including 18 months following the approval in accordance with Section 505B (i) (1) of the Food and Drug Cosmetic Act [21 U.S.C. §355c]. The trigger for this pediatric postmarketing safety review was the approval of BLA supplement 125163/405 on November 18, 2016 for use of FluLaval Quadrivalent in persons 6 to 35 months.

This memorandum documents the Food and Drug Administration's (FDA's) complete evaluation, including review of adverse event (AE) reports in passive surveillance data, periodic safety reports from the manufacturer, data mining, and a review of the published literature.

1.2 Product Description

FluLaval Quadrivalent is an inactivated vaccine indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. FluLaval Quadrivalent is approved for use in persons aged 6 months and older[1].

FluLaval Quadrivalent (hereby referred to as FluLaval QIV) is a split virion, seasonal influenza vaccine containing the purified outer membrane protein hemagglutinin (HA) from each of four influenza virus strains. The HA antigens are derived from viruses propagated in embryonated chicken eggs. Each dose contains 60micrograms (mcg) HA in the recommended ratio of 15mcg HA of each of the 4 influenza strains. This vaccine is presented as a suspension for intramuscular injection supplied in 0.5mL single-dose, prefilled syringes and 5mL multi-dose vials. The prefilled syringe is formulated without preservatives and does not contain thimerosal. Each 0.5mL dose from the multi-dose vial contains 50mcg thimerosal (<25 mcg mercury); thimerosal, a mercury derivative, is added as a preservative.

Specific vaccine strain composition for all seasonal influenza vaccines are determined annually by the FDA's Vaccines and Related Biological Products Advisory Committee, taking into consideration recommendations from the World Health Organization. The Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) provides and periodically updates recommendations for use of seasonal influenza vaccinations.[2]

Trivalent vs. Quadrivalent Formulations of Seasonal Influenza Vaccines

[1] FluLaval Quadrivalent U.S. package insert; updated February 6, 2020

[2] Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2019–20 Influenza Season. Lisa A. Grohskopf, MD; Elif Alyanak; Karen R. Broder; Emmanuel B. Walter; Alicia M. Fry; Daniel B. Jernigan. Morbidity and Mortality Weekly Report. August 23, 2019 / 68(3);1–21.Available at https://www.cdc.gov/mmwr/volumes/68/rr/rr6803a1.htm

Trivalent (three-strain) influenza vaccines protect against the strains expected to be predominant in humans in a given year: two subtype A virus strains and a type B strain. Two influenza B virus lineage strains circulate to varying degrees each year making it difficult to predict which one will predominate in a particular influenza season. Quadrivalent (four-strain) influenza vaccine formulations are designed to protect against both influenza B strains, providing additional coverage.

1.3 Regulatory History

- August 15, 2013: FDA approval of STN 125163/253 to include a quadrivalent influenza virus vaccine formulation (i.e., FluLaval QIV) for the prevention of influenza disease in persons 3 years of age or older
    - This approval triggered a prior presentation to the 2016 PAC for the review period August 15, 2013 – June 30, 2015
- November 18, 2016: FDA granted approval of STN 125163/405 for use of FluLaval QIV in persons 6 to 35 months
    - This approval is the trigger for the presentation to the 2020 PAC for the review period November 18, 2016 – February 29, 2020

2 MATERIALS REVIEWED

- Vaccine Adverse Events Reporting System (VAERS)
    - VAERS reports for FluLaval QIV during November 18, 2016 to February 29, 2020 (PAC review period)
- Manufacturer's Submissions
    - FluLaval QIV U.S. package insert; updated February 6, 2020
    - Applicant response to information request regarding dose distribution data, received April 30, 2020
    - Pharmacovigilance Plan, version 2, dated January 2016
    - Periodic safety reports
- FDA Documents
    - STN 125163/405 FluLaval Quadrivalent Approval Letter, dated November 18, 2016
    - STN 125163/405 OBE/DE Pharmacovigilance Plan Review Memorandum
- Publications (see Literature Search in Section 7)

3 LABEL CHANGES IN REVIEW PERIOD

There were no label changes related to safety concerns during the review period.

4 PRODUCT UTILIZATION DATA

GSK provided estimates of FluLaval QIV distribution data for the US and worldwide (i.e., outside of the US) for the PAC review period:

Total doses distributed in the US was 62,803,000 doses.

Period	2016*	2017	2018	2019	2020**	Total
Doses (thousands)	73	19,090	21,880	21,635	125	62,803

*November and December only
**January and February

Total doses distributed worldwide was 9,432,000 doses.

Period	2016*	2017	2018	2019	2020**	Total
Doses (thousands)	0	1,312	3,530	4,550	41	9,432

*November and December only
**January and February

The sponsor was not able to provide data on proportion of doses distributed to pediatric and adult patients. Note that the number of doses distributed is an estimate of the number of patients vaccinated because doses may have been distributed without being administered to patients or patients may have received more than one dose.

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan

The manufacturer's current Pharmacovigilance Plan (PVP), version 2, dated January 2016, lists the following important identified and potential risks, and missing information for FluLaval QIV (see Table 1):

Table 1: FluLaval QIV Safety Concerns

Important Identified Risks
None
Important Potential Risks
Anaphylaxis
Febrile seizure
Bell's Palsy
Guillain-Barré Syndrome
Injection site hemorrhage in individuals with thrombocytopenia or any other coagulation disorder
Narcolepsy
Missing Information
Use during pregnancy
Use during lactation

Anaphylaxis: Allergic reactions including anaphylaxis have been reported with FluLaval QIV and is labeled in section *6.2 Postmarketing Experience*. FluLaval QIV is contraindicated in anyone with a history of severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine, including egg protein, or following a previous dose of any influenza vaccine (labeled in section 4 *Contraindications*).

Febrile seizure: Febrile seizures were detected in young children in Western Australia in association with another seasonal vaccine in 2010.[3, 4]

Bell's palsy: Bell's palsy has been associated with use of an E. coli heat-labile toxin-containing intranasal inactivated influenza vaccine, never licensed or distributed within the US, which was withdrawn from the market.[5]A subsequent, well-designed epidemiological study did not show an association with other inactivated influenza vaccines and the development of Bell's palsy.[6]

Guillain-Barré Syndrome: Guillain-Barré Syndrome (GBS) is labeled in section 5 *Warnings and Precautions*. GBS was associated with use of an A/New Jersey 1976 influenza vaccine in anticipation of a swine influenza epidemic, and is routinely listed in the label of influenza vaccines.[7]

Narcolepsy: In 2014, the manufacturer added narcolepsy as a potential risk to its Risk Management Plan (RMP) in Europe (the RMP is the pharmacovigilance plan document

[3] Armstrong PK, Dowse GK, Effler PV, et al. Epidemiological study of severe febrile reactions in young children in Western Australia caused by a 2010 trivalent inactivated influenza vaccine. BMJ 2011;1:e000016.
[4] Therapeutic Goods Administration. Seasonal flu vaccine: Overview of vaccine regulation and safety monitoring and investigation into adverse events following 2010 seasonal influenza vaccination in young children. Available: https://www.tga.gov.au/alert/seasonal-flu-vaccine-overview-vaccine-regulation-and-safety-monitoring-and-investigation-adverse-events-following-2010-seasonal-influenza-vaccination-young-children
[5] Mutsch M, Zhou W, Rhodes P, et al. Use of the inactivated intranasal influenza vaccine and the risk of Bell's palsy in Switzerland. N Engl J Med 2004;350:896-903.
[6] Stowe J, Andrews N, Wise L, et al. Bell's palsy and parenteral inactivated influenza vaccine. Human Vaccines 2006;2:110-2.
[7] Schonberger LB, Bregman DJ, Sullican-Bloyai JZ, et al. Guillain-Barré syndrome following vaccination in the National Influenza Immunization Program, United States, 1976-1977. Am J Epidemiol 1979;110:105-23.

used in Europe) for all of its H1N1-containing influenza vaccines, noting that this change was a precautionary measure based on epidemiological studies that reported an increased risk of narcolepsy in subjects who received GSK's pandemic vaccine, Pandemrix. The sponsor notes that there is no clinical evidence of increased risk of narcolepsy for GSK H1N1-containing seasonal influenza vaccines, including FluLaval QIV.

The identified and potential risks listed in Table 1 are common to this product class and will be monitored with routine safety surveillance, including review of adverse event reports submitted to FDA, manufacturer submitted periodic safety reports, published literature, and data mining. There are no postmarketing requirement (PMR) safety-related studies under FDAAA or Risk Evaluation and Mitigation Strategy (REMS) for FluLaval QIV. The sponsor is also conducting a pregnancy registry study (please see section 5.2).

5.2 Postmarketing Studies

Pregnancy registry: Applicant is conducting the following combined pregnancy registry for GSK inactivated influenza vaccines (FluLaval, FluLaval QIV, Fluarix, Fluarix QIV):

- An exploratory prospective, cohort study (Protocol EPI-FLU-039) to detect and describe abnormal pregnancy outcomes in women intentionally or unintentionally vaccinated with Fluarix or Fluarix Quadrivalent or FluLaval or FluLaval Quadrivalent during pregnancy or within 28 days preceding conception.
- Status: Ongoing. [Final study report submission date: May 31, 2020]

6 ADVERSE EVENT REVIEW

6.1 Methods

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event reports following use of FluLaval QIV between November 18, 2016 to February 29, 2020. VAERS stores postmarketing adverse events and medication errors submitted to FDA and CDC for all approved vaccines. These reports originate from a variety of sources, including healthcare providers, consumers, and manufacturers. Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in VAERS may not be medically confirmed and are not verified by FDA. FDA does not receive reports for every adverse event or medication error that occurs with a vaccine. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Also, there is no certainty that the reported event was actually due to the vaccine.

6.2 Results

The results of the VAERS search of AE reports for FluLaval QIV during the PAC review

period are listed in Table 2 below. There were 2,474 US and 24 foreign reports for review period November 18, 2016 to February 29, 2020.

Table 2: FluLaval QIV VAERS reports during November 18, 2016 – February 29, 2020

Age	Serious non-fatal, US	Serious Non-fatal, Foreign	Deaths, US	Deaths, Foreign	Non-Serious, US	Non-Serious, Foreign	Total, US	Total, Foreign
<18 years	56	1	4	0	1198	0	1258	1
≥18 years	70	3	3	0	965	0	1038	3
Unknown	20	20	1	0	157	0	178	20
All ages	146	24	8	0	2320	0	2474	24

Note: Serious non-fatal adverse events include life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, or significant disability, and otherwise medically important conditions (OMIC).

6.2.1 Deaths

There were 8 deaths reported of patients post receipt of FluLaval QIV during the PAC review period, including 4 pediatric deaths. Patient ages ranged between 6 months and 68 years. The fatal reports were individually reviewed and are summarized below.

Pediatric Deaths

1. This was a death in a 15-month-old otherwise healthy male infant who was found unresponsive (b) (6) weeks post receipt of Diphtheria, Tetanus, Pertussis (Infanrix) Haemophilus influenza type b (Hiberix), Pneumococcal conjugate vaccine (Prevnar13) and FluLaval QIV vaccines. Patient was found by his mother in the morning, lying face down on a mattress he had shared that night with two older siblings. He was found lying on top of the blanket, with his head on a pillow and turned slightly to the side. Life support efforts were unsuccessful, and he was found to be in cardiac arrest and pronounced dead on arrival. An autopsy was performed, and the final cause of death was reported as Sudden Unexpected Infant Death (SUID).

Reviewer Comment: SUID, including SIDS, is further discussed below. Despite the relatively close temporal proximity between receipt of vaccines and death, receipt of Flulaval QIV is unlikely to be the cause of death in this 15-month-old.

2. This was a death in a 7-month-old male infant (b) (6) post receipt of FluLaval QIV. The child was found unresponsive and pulseless in bed, sandwiched between bed and pillows. Patient found to be in cardiopulmonary arrest, was intubated initially, but made Do Not Resuscitate (DNR) once brain death was established. Etiology of death was thought to be secondary to asphyxia.

<u>Reviewer Comment</u>: This patient death was secondary to asphyxia, and not likely related to receipt of FluLaval QIV (b) (6) *prior.*

3. This was a death in a 15-month-old previously healthy female infant found unresponsive in bed (b) (6) days post receipt of Haemophilus influenza type b (ActHIB), Pneumococcal conjugate vaccine (Prevnar13) and FluLaval QIV vaccines. CPR was performed unsuccessfully, and patient was pronounced dead on arrival. No autopsy findings or further information was available in the report.

<u>Reviewer Comment</u>: This case is consistent with SUID (further discussed below). Despite the relatively close temporal proximity between receipt of vaccines and death, receipt of FluLaval QIV is unlikely to be the cause of death in this 15-month-old.

4. This was a death in a 15-month-old male patient (b) (6) days post receipt of Varicella (Varivax) and FluLaval QIV vaccines. The patient reportedly had a post vaccination fever to 102.5ºF on day 2 post vaccination, and vomiting 5 days post vaccination. The patient was found to be in cardiopulmonary arrest (b) (6) days post vaccination, and further resuscitation efforts failed. The final cause of death from an autopsy report was myocarditis of probable viral etiology.

<u>Reviewer Comment</u>: This patient death was due to cardiopulmonary arrest secondary to myocarditis and not likely related to receipt of FluLaval QIV (b) (6) *days prior.*

Sudden infant death syndrome [SIDS]: Approximately 3500 infants die annually in the United States from sleep-related infant deaths, including sudden infant death syndrome (SIDS), ill-defined deaths, and accidental suffocation and strangulation in bed.[8] Sudden unexpected infant death (SUID) is a term used to describe any sudden and unexpected death, whether explained or unexplained (including SIDS and ill-defined deaths), occurring during infancy. SIDS is a subcategory of SUID. SIDS is the sudden unexpected death of an apparently healthy infant younger than age 12 months whose cause of death remains unknown despite a death scene investigation, a review of the clinical history, and an autopsy.[9] SIDS remains one of the leading causes of infant death in the United States. It is reported that the US SIDS rate was 40 deaths per 100,000 live births in 2013.[10] The Institute of Medicine has reviewed the topic of SIDS

[8] Moon RY; TASK FORCE ON SUDDEN INFANT DEATH SYNDROME. SIDS and Other Sleep-Related Infant Deaths: Evidence Base for 2016 Updated Recommendations for a Safe Infant Sleeping Environment.
[2] Goldberg N, Rodriguez-Prado Y, Tillery R, Chua C. Sudden Infant Death Syndrome: A Review. Pediatr Ann. 2018 Mar 1;47(3):e118-e123.
[9] Goldberg N, Rodriguez-Prado Y, Tillery R, Chua C. Sudden Infant Death Syndrome: A Review. Pediatr Ann. 2018 Mar 1;47(3):e118-e123.
[10] Moon RY; TASK FORCE ON SUDDEN INFANT DEATH SYNDROME. SIDS and Other Sleep-Related Infant Deaths: Evidence Base for 2016 Updated Recommendations for a Safe Infant Sleeping Environment.

and concluded, “The evidence favors rejection of a causal relationship between exposure to multiple vaccines and SIDS.” [11]

Adult Patient Deaths

1. This was a death in 68-year-old male patient (b) (6) months post receipt of FluLaval QIV. The patient was diagnosed with and admitted for treatment of GBS with IVIG 1 week post vaccination. He developed complications while inpatient, including bilateral pneumonia, respiratory failure, septic shock and renal failure. Cause of death was reported as GBS, renal failure and septic shock.

2. This was a death in a 64-year-old female patient (b) (6) days post receipt of FluLaval QIV. The patient was reported to have atherosclerotic disease, with cause of death reported as sudden cardiac death. No other information was available in report.

3. This was a death in an 18-year-old male patient with preexisting cerebral palsy, (b) (6) days post receipt of FluLaval QIV. The patient was brought to urgent care with vague abdominal discomfort, lethargy, and actively having tonic clonic seizures upon presentation. He aspirated significantly post seizure, leading to respiratory arrest and eventual cardiac arrest. CPR was administered unsuccessfully, and cause of death was reported as cardiac arrest and seizure.

4. This was a death in a 78-year-old female patient within a year of receipt of Flulaval QIV. The patient reportedly lived in a skilled nursing facility, and developed shingles at an unknown date post receipt of FluLaval QIV. The patient was started on Valtrex and died of multiple organ dysfunction at an unknown time afterwards. No more information was available from the reporter or from GSK.

Reviewer Comments on adult deaths: All 4 adult deaths had known etiologies within each narrative, including patients with preexisting conditions making them susceptible to the final cause of death. There was no information in the narratives to directly link these deaths to receipt of FluLaval QIV.

6.2.2 Serious Non-fatal Reports

During the PAC review period, there were 171 serious non-fatal reports. Fifty-seven serious non-fatal reports involved pediatric patients, of which there were 56 US reports and a single foreign report. Adult serious non-fatal reports included 70 US reports and 3 foreign reports. Age was unknown for the remaining 40 serious non-fatal reports.

[11] Immunization Safety Review: Vaccinations and Sudden Unexpected Death in Infancy. Stratton KR, Almario DA, Wizemann TM, and McCormick MC (eds). Washington, DC: National Academy Press, 2003

The most common Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) are displayed for pediatric and adult patients (see Tables 3 and 4). Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 3: Most frequently reported PTs for pediatric (< 18 years) serious non-fatal reports

Preferred Tern (PT)	**# Serious Pediatric Reports**	***Label Status** **Label dated February 6, 2020 (Label Section)*
PYREXIA	20	Labeled (6.1)
VOMITING	16	Labeled (6.1)
SEIZURE	13	Labeled (6.2)
INTENSIVE CARE	11	Not applicable
UNRESPONSIVE TO STIMULI	11	Unlabeled
CRYING	10	Labeled (6.1)
IRRITABILITY	10	Labeled (6.1)
TACHYCARDIA	10	Unlabeled
DIARRHOEA	9	Labeled (6.1)
GAIT DISTURBANCE	9	Labeled (6.2)
IMMUNOGLOBULIN THERAPY	9	Not applicable
ENDOTRACHEAL INTUBATION	8	Not applicable
HYPOTONIA	8	Unlabeled
LETHARGY	8	Unlabeled
PAIN IN EXTREMITY	8	Labeled (6.2)

6.1 Clinical Trials Experience; 6.2: Postmarketing Experience
Note: PTs occurring with a frequency >7 reports are shown in above table.

Reviewer comments: Most PTs are labeled events or consistent with an already labeled event. *Discomfort* is related to pain. *Intensive care* (describing hospital setting), *Endotracheal intubation* (describing a procedure) and *Immunoglobulin therapy* (treatment) are not adverse events. *Tachycardia*, *Unresponsive to stimuli, Lethargy* and *Hypotonia* are non-specific events and may occur in association with multiple conditions.

Table 4: Most frequently reported PTs for adult (≥ 18 years) serious non-fatal reports

Preferred Tern (PT)	**# Serious Adult Reports**	***Label Status** **Label dated February 6, 2020 (Label Section)*
PAIN	21	Labeled (6.1)
HEADACHE	16	Labeled (6.1)
DYSPNOEA	15	Labeled (6.2)
TACHYCARDIA	15	Unlabeled
ASTHENIA	14	Labeled (6.2)
INJECTION SITE PAIN	14	Labeled (6.2)
PAIN IN EXTREMITY	14	Labeled (6.2)

Preferred Tern (PT)	# Serious Adult Reports	*Label Status *Label dated February 6, 2020 (Label Section)*
MUSCULOSKELETAL PAIN	13	Labeled (6.2)
DIZZINESS	12	Labeled (6.2)
HYPOAESTHESIA	12	Labeled (6.2)
PARAESTHESIA	12	Labeled (5.2)
PYREXIA	12	Labeled (6.1)
INTENSIVE CARE	9	Not applicable
MUSCULAR WEAKNESS	9	Labeled (6.2)
NAUSEA	9	Labeled (6.1)
CHILLS	8	Labeled (6.1)
CONDITION AGGRAVATED	8	Not applicable
GUILLAIN-BARRE SYNDROME	8	Labeled (5.1)
JOINT RANGE OF MOTION DECREASED	8	Unlabeled

5.1: Warnings and Precautions (Guillain-Barré Syndrome); 5.2: Warnings and Precautions (Syncope); 6.1 Clinical Trials Experience; 6.2: Postmarketing Experience
Note: PTs occurring with a frequency >7 reports are shown in above table.

Reviewer comments: Most commonly reported PTs are labeled. *Intensive* care and *Condition aggravated* are not adverse events. *Tachycardia* and *Joint range of motion decreased* are non-specific events and may occur in association with multiple underlying conditions.

6.2.3 Non-serious Reports

During the reporting period, there were 2,320 non-serious reports; 1,198 of which involved pediatric patients. Table 5 below lists the 10 most frequently reported PTs in non-serious reports. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 5: Ten most frequently reported PTs in non-serious reports

Preferred Term (PT)	# Non-serious Reports	*Label Status *Label dated February 6, 2020 (Label Section)*
INJECTION SITE ERYTHEMA	345	Labeled (6.1)
INJECTION SITE PAIN	278	Labeled (6.1)
INJECTION SITE SWELLING	244	Labeled (6.1)
PRODUCT STORAGE ERROR	220	Not applicable
PAIN	207	Labeled (6.1)
PYREXIA	207	Labeled (6.1)
ERYTHEMA	204	Labeled (6.1)
PAIN IN EXTREMITY	201	Labeled (6.2)

Preferred Term (PT)	# Non-serious Reports	*Label Status *Label dated February 6, 2020 (Label Section)*
URTICARIA	165	Labeled (6.2)
INJECTION SITE WARMTH	164	Unlabeled
DIZZINESS	150	Labeled (6.2)

6.1 Clinical Trials Experience; 6.2: Postmarketing Experience

Reviewer comments: The majority of frequently reported PTs associated with non-serious reports are labeled. *Product storage error* is not an adverse event; screening of reports showed that cases involved situations where the vaccine had been stored at a temperature that was out of range. As per the package insert, recommended storage conditions include refrigeration between 2º and 8ºC (36º and 46ºF). *Injection site warmth* is related to other labeled events describing injection site reactions.

6.3 Data mining

Data mining was performed to evaluate whether any reported events following the use of FluLaval QIV were disproportionally reported compared to other vaccines in the VAERS database. The background database contains VAERS reports since 1990. Disproportionality alerts do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation. A query of Empirica Signals Management with the US VAERS Vac Name run with a data lock date of April 28, 2020 for INFLUENZA (SEASONAL) (FLULAVAL QUADRIVALENT) did not identify any PTs with a disproportional reporting alert (EB05>2; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean).

6.4 Periodic safety reports

The manufacturer's postmarketing periodic safety reports for FluLaval QIV were reviewed. The AEs reported were consistent with those seen in VAERS. No additional safety issues were identified, and no actions were taken by the sponsor for safety reasons.

7 LITERATURE REVIEW

A search of the US National Library of Medicine's PubMed.gov database on April 14, 2020 for peer-reviewed literature, with the search term "FluLaval Quadrivalent" and "safety" limited by human species, and dates from PAC trigger (November 18, 2016) to date of search (April 14, 2020), retrieved 1 publication pertaining to safety. No new safety concerns for FluLaval QIV were identified in the review of this publication, summarized in the table below:

Publication	Authors' Safety Conclusion
Jain VK, Domachowske JB, Wang L et al. *Time to Change Dosing of Inactivated Quadrivalent Influenza Vaccine in Young Children: Evidence From a Phase III, Randomized, Controlled Trial.* J Pediatric Infect Dis Soc. 2017 Mar 1;6(1):9-19	Flulaval QIV had similar safety and reactogenicity, including fever, to Fluzone® despite the higher antigen content and volume. There were no attributable serious adverse events.

8 CONCLUSION

This postmarketing pediatric safety review was triggered by the November 18, 2016 approval for use of FluLaval QIV in persons 6 to 35 months. Review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for FluLaval QIV does not indicate any new safety concerns. Adverse events were generally consistent with the safety data in pre-licensure studies and listed in the label. No unusual frequency, clusters, or other trends for adverse events were identified that would suggest a new safety concern.

9 RECOMMENDATIONS

FDA recommends continued routine safety monitoring of FluLaval Quadrivalent.