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

MEMORANDUM

To:	Craig Zinderman, MD, MPH Associate Director for Medical Policy Office of Biostatistics and Pharmacovigilance (OBPV) Center for Biologics Evaluation and Research (CBER)
From:	Jonathan Reich, MD Medical Officer, Pharmacovigilance Branch 2 (PB2) Division of Pharmacovigilance (DPV), OBPV, CBER Meghna Alimchandani, MD Deputy Director, DPV, OBPV, CBER
Subject:	Safety and Utilization Review for the Pediatric Advisory Committee
Applicant:	Glaxosmithkline Biologicals (GSK)
Product:	Fluarix Quadrivalent (influenza vaccine)
STN:	125127/1106
Indication:	Fluarix Quadrivalent is indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. Fluarix Quadrivalent is approved for use in persons aged 6 months and older.
Meeting Date:	Pediatric Advisory Committee Meeting, April 2023

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 product 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 STN 125127/834 to extend the age range for use of Fluarix Quadrivalent to include children 6 to 35 months of age.

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 Indication and Product Description

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

Fluarix Quadrivalent (hereafter referred to as Fluarix QIV) is a split virion, seasonal influenza vaccine. The Fluarix QIV hemagglutinin antigens (HA) 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) HA in the recommended ratio of 15 mcg HA of each of the 4 influenza strains in a sterile, buffered aqueous suspension.

Specific vaccine strain composition for all seasonal influenza vaccines is 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

Fluarix QIV is manufactured using the same process as that for Fluarix trivalent formulation. Trivalent (three-strain) influenza vaccines protect against the strains expected to be predominant in humans each 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

[1] Fluarix Quadrivalent U.S. package insert; updated July 1, 2022
[2] Grohskopf LA, Blanton LH, Ferdinands JM, et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season. MMWR Recomm Rep 2022;71(No. RR-1):1–28. DOI: http://dx.doi.org/10.15585/mmwr.rr7101a1

season. In addition to protection against influenza A strains, quadrivalent (four-strain) influenza vaccine formulations are designed to also protect against both influenza B strains, providing additional coverage.

1.3 Regulatory History

- December 14, 2012: Approval of STN 125127/513 to include a quadrivalent influenza virus vaccine formulation for use of Fluarix QIV in persons 3 years of age and older.
    - Trigger for a previous PAC review under STN 125127/702
- January 11, 2018: Approval of STN 125127/834 to extend the age range for use of Fluarix QIV to include children 6 to 35 months of age
    - Regulatory trigger for current PAC review

2 MATERIALS REVIEWED

- Vaccine Adverse Events Reporting System (VAERS)
    - VAERS reports for Fluarix QIV during January 11, 2018 to October 31, 2022 (PAC review period)
- Manufacturer's Submissions
    - Fluarix QIV U.S. package insert; updated July 1, 2022
    - Applicant response to information request regarding dose distribution data, received under STN 125127/1106
    - Pharmacovigilance Plan, Version 10.0, dated July 13, 2016
    - Periodic safety reports
- FDA Documents
    - STNs 125127/513 and 125127/834 Fluarix QIV approval letters
    - STN 125127/834 Pharmacovigilance Plan Review Memorandum
- Publications (see Literature Search in Section 7)

3 LABEL CHANGES IN REVIEW PERIOD

During the PAC review period, the following label change was associated with postmarketing safety data:

- On March 16, 2018, a labeling supplement was approved under STN 125127/873 to revise the USPI to include the term "influenza-like illness" under Section 6.2 *Postmarketing Experience.*

4 PRODUCT UTILIZATION DATA

GSK provided estimates of Fluarix QIV distribution data for the US and worldwide for

the PAC review period:

The net total numbers of doses of vaccine distributed for the US, including Puerto Rico:
For the US, including Puerto Rico:

Period	2018*	2019	2020	2021	2022**	Total
Doses (million)	21.18	25.03	28.06	25.86	15.49	115.5

*Entire year
**To October 01, 2022.

The net total numbers of doses of vaccine distributed worldwide, including the US:

Period	2018*	2019	2020	2021	2022**	Total
Doses (millions)	39.67	42.11	53.47	53.16	30.28	218.7

* Entire year
** To October 01, 2022.

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.

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan

The manufacturer's current Pharmacovigilance Plan (PVP), Version 10.0, dated July 13, 2016, lists the following important potential risks and missing information for Fluarix QIV (see Table 1). There are no important identified risks in the PVP.

Table 1: Fluarix QIV Safety Concerns

Important Potential Risks
Anaphylaxis
Febrile seizure
Bell's palsy
Guillain-Barré syndrome (GBS)
Injection site hemorrhage in individuals with thrombocytopenia or any other coagulation disorder
Administration error due to mix-up of vaccine brands
Narcolepsy
Missing Information
Use during pregnancy and lactation

Anaphylaxis: Anaphylaxis is labeled under section 6.1 *Clinical Trials Experience* (there was a single case of anaphylaxis within one day following administration of the trivalent formulation of Fluarix). Fluarix QIV is contraindicated in individuals with a history of severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine, including egg protein, or following a previous administration of any influenza vaccine and labeled under section 4 *Contraindications* of the USPI.

Febrile seizure: Febrile seizures were detected in young children in Western Australia in association with a different influenza vaccine in 2010.[3, 4] Convulsion is labeled under section *6.2 Postmarketing Experience.*
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] Facial palsy and facial paresis are labeled under section *6.2 Postmarketing Experience.*

Guillain-Barré Syndrome: Guillain-Barré Syndrome (GBS) is labeled in section 5 *Warnings and Precautions* and section *6.2 Postmarketing Experience.*
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]

Injection site hemorrhage in individuals with thrombocytopenia or any other coagulation disorder: Information is included for "Persons at Risk of Bleeding" under Section 5 *Warnings and Precautions* of the USPI. Fluarix QIV should be given with caution in individuals with bleeding disorders, such as hemophilia or on anticoagulant therapy, to avoid the risk of hematoma following the injection.

Administration error due to mix-up of vaccine brands: The sponsor considers administration error due to mix-up of vaccine brands as a potential risk because GSK co-markets Fluarix and Fluarix QIV in certain countries.

Narcolepsy: Narcolepsy was not reported in clinical trials. GSK considers narcolepsy a potential risk based on prior epidemiological studies. As per the PVP, "*Several epidemiological studies reported an increased risk of narcolepsy in subjects with Pandemrix (an AS03-adjuvanted monovalent H1N1 vaccine) vaccination or H1N1*

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[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.

infection. A literature article published in December 2013[8] reported results from a study investigating the autoimmune basis at the cellular level for the development of narcolepsy and its relationship to the 2009 pandemic H1N1 influenza A strain which was included in H1N1-containing pandemic and seasonal influenza vaccines. Based on these results, although to date, there has been no clinical evidence that vaccination with H1N1-containing seasonal vaccines increases the risk of narcolepsy, out of an abundance of caution, GSK has decided to add narcolepsy as a potential risk to the Risk Management Plan for FLU D- QIV.V."

The potential risks listed in Table 1 are 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 Fluarix QIV. The sponsor has completed a pregnancy registry as a postmarketing commitment (PMC) study (please see section 5.2).

5.2 Postmarketing Studies

The following postmarketing studies were described in STN 125127/513 approval letter dated December 14, 2012.

Postmarketing requirement under Pediatric Research Equity Act (PREA)

- *Deferred pediatric study D-QIV-004 under PREA for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in Fluarix® Quadrivalent, in pediatric patients ages 6 months to 35 months of age.*

Study status: Fulfilled

The applicant has fulfilled the pediatric study requirement for all relevant pediatric age groups for this application.

Postmarketing commitment (PMC)

- *To establish a pregnancy registry to prospectively collect data on spontaneously-reported exposures to Fluarix® Quadrivalent during pregnancy. A protocol for this pregnancy registry will be submitted by April 30, 2013. The pregnancy registry will be established by August 30, 2013 and annual reports will be submitted with the periodic safety update reports (PSURs) for Fluarix® Quadrivalent. When the registry has collected data on the outcomes specified in the protocol for five years, GSK will submit a full study report 18 months from submission of the fifth annual PSUR. After submission of the registry report,*

[8] De la Herran-Arita A.K., Rahbek Kornum B., Mahlios J. CD4+ T Cell Autoimmunity to Hypocretin/Orexin and Cross-Reactivity to a 2009 H1N1 Influenza A Epitope in Narcolepsy. Science Translational Medicine 2013: 5(216): 216ra176

GSK will continue enrolling in the registry pending CBER review of the report and determination that the registry can be discontinued.

Study status: Final Study Report (FSR) was submitted and reviewed under STN 125127/1007, and this PMC has been fulfilled. The last patient was enrolled in May 2019 and the final report was received in June 2020. Approximately 21% of the enrolled patients had pregnancy results at the time of the study report and no safety signal was identified.

6 ADVERSE EVENT REVIEW

6.1 Methods

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event reports following use of Fluarix QIV between January 11, 2018 to October 31, 2022 (PAC review period). 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 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 solely due to the vaccine.

6.2 Results

The results of the VAERS search of AE reports for Fluarix QIV during the PAC review period are listed in Table 2 below. There were 6,106 US and 355 foreign reports for the review period January 11, 2018 to October 31, 2022.

Table 2: Fluarix QIV VAERS reports during January 11, 2018 to October 31, 2022

Age	Serious Non-Fatal*		Deaths		Non-Serious		Total Reported	
	US	Foreign	US	Foreign	US	Foreign	US	Foreign
<18 years	95	35	4	0	1195	1	1294	36
≥ 18 years	325	124	11	10	3783	7	4119	141
Unknown	170	165	14**	13**	509	0	693	178
All Ages	590	324	29	23	5487	8	6106	355

*Note: Serious non-fatal adverse events include life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, or significant disability or otherwise medically important conditions (OMIC).
** Upon manual review of narratives, 8 reports contained patient age. Please see section 6.2.1 for complete details.

6.2.1 Deaths

There were 50 deaths reported during the PAC review period, including 4 pediatric deaths (U.S. reports). These reports were individually reviewed and are summarized below (two death reports were duplicates).

Pediatric death reports

- 11-year-old female received 4 vaccinations, three days later she presented to the emergency room in septic shock. She died that day after unsuccessful attempts at resuscitation.
- 15-month-old male infant found dead in his crib three days following receipt of three vaccines.
- 1-year-old male infant was vaccinated with Fluarix QIV and four other vaccines. He suffered an anoxic encephalopathy approximately three months following vaccination. He died a week later.
- 10-year-old male with a known history of asthma, who had tolerated the flu vaccine in the past, died of an asthma attack two days after receiving Fluarix QIV and Nucala (Mepolizumab-a monoclonal antibody for eosinophilic asthma). It was the only vaccine he received at that visit.

Reviewer comment: There were no reports of pediatric deaths that were attributed to Fluarix QIV based on FDA review of the above cases.

Adult death reports

During the PAC review period, there were 27 adult death reports (13 U.S. reports and 14 foreign reports).

U.S. adult death reports

The only diagnosis observed more than once was acute respiratory failure. These three patients include:

- 44-year-old woman whose report contained limited information. It describes her demise from acute respiratory failure and an unsuccessful ECMO trial. She died five days after getting vaccinated.
- 88-year-old male presented to his primary care provider 2 months after his vaccination with a runny nose and watery eyes. This progressed to a respiratory failure not otherwise specified.
- A patient 85 years of age who died more than a year after vaccination from bronchitis.

Of note, is the case of a 71-year-old female who died of complications of Guillain-Barre Syndrome.

The other 9 cases consist of a case of sudden death, a coma the day after vaccination, acute mental status changes in an 89-year-old, sepsis 3 weeks after vaccination, an immunocompromised patient who died 6 weeks after vaccination, a case of anaphylaxis, a patient who experienced chills and fever and then died 15 days after vaccination, and a patient who died from co-existing congestive heart and kidney failure. There is also a 58-year-old male, with unknown cause of death, for whom limited information is provided.

Foreign Adult Death Reports: There were 14 foreign death reports for which the age is known. Two patients (a 60 year old male and a 74 year old female) died of influenza infection[9], an 81-year-old woman died of complications of Guillain-Barre Syndrome, and a 75-year-old woman died of cancer.

Cerebrovascular accident or a neurologic condition which may have been caused by a cerebrovascular accident were described in 4 reports, with 3 of the patients older than 81 years of age. There were two cases of cardiac arrest, one in a patient with 3 previously placed coronary stents. The other 4 cases include a case of an allergic reaction, sepsis, influenza infection[9], and two cases in which the cause of death was unknown.

<u>Death reports: patient age unknown</u>

Patient age is not reported for the remaining 19 death reports (12 U.S. reports; 7 foreign reports).

Domestic cases: Of these 12 remaining cases, 6 deaths are of unknown cause. Three deaths are reported to be related to influenza[9]. There were 2 additional cases of death from complications of Guillain-Barre Syndrome and a case of death from pneumonia.

Foreign cases: For these 7 cases there were 3 cases of unknown etiology, a death secondary to a stroke, and 3 cases of influenza infection[9].

Reviewer comments: There were 4 cases of deaths from complications of Guillain-Barre Syndrome. GBS is included in *Warnings and Precautions* and *Postmarketing*

[9] Fluarix QIV USPI includes section 5.5 *Limitations of Vaccine Effectiveness,* which states that "Vaccination with FLUARIX QUADRIVALENT may not protect all susceptible individuals."

Experience sections of the USPI. Reports of adult deaths that attributed to Fluarix QIV based on FDA review had underlying conditions and comorbidities that were contributing factors, and alternative etiologies were present.

6.2.2 Serious Non-fatal Reports

During the PAC review period, there were 914 serious non-fatal reports, including 130 pediatric reports and 449 adult reports. Age was unknown for the remaining 335 reports.

The most common Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) for pediatric reports are displayed in Table 3. 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 Term (PT)	**# Serious Pediatric Reports**	***Label Status** **Label dated July 1, 2022 (Label Section)*
Pyrexia	135	Section 6.1
Influenza	114	Section 6.1
Pain	110	Adverse Reactions, Section 6.1
Vaccination failure	107	Limitations of Vaccine Effectiveness, Section 5.5
Pain in Extremity	92	Section 6.1
Dyspnea	85	Section 6.2
Headache	82	Adverse Reactions, Section 6.1
Guillain-Barre Syndrome	86	Warnings and Precautions
Dizziness	74	Warnings and Precautions
Muscular Weakness	71	Adverse Reactions, Section 6.1
Asthenia	71	Section 6.2
Hypoaesthesia	67	Section 6.2
Fatigue	65	Adverse Reactions, Section 6.1
Paresthesia	65	Section 5.2, Section 6.2
Injection Site Pain	64	Adverse Reactions, Section 6.1

Note: PTs occurring with a frequency >64 reports are shown in above table.

Reviewer comments: Most frequently reported PTs are labeled events. The PT for *Vaccination failure* is related to information describing *Limitations of Vaccine Effectiveness,* section 5.5, which states that "Vaccination with FLUARIX QUADRIVALENT may not protect all susceptible individuals."

The most common PTs for adult reports are displayed in Table 4. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 4: Most frequently reported PTs for adult serious non-fatal reports

Preferred Term (PT)	# Serious Adult Reports	*Label Status *Label dated July 1, 2022 (Label Section)*
Pain	78	Adverse Reactions, Section 6.1
Pyrexia	66	Section 6.1
Pain in Extremity	62	Adverse Reactions, Section 6.1
Headache	57	Adverse Reactions, Section 6.1
Injection Site Pain	54	Adverse Reactions, Section 6.1
Dizziness	54	Warnings and Precautions
Hypoaesthesia	53	Section 6.2
Muscular Pain	53	Adverse Reactions, Section 6.1
Paraesthesia	53	Section 5.2, Section 6.2
Dyspnea	49	Section 6.2
Nausea	47	Section 6.1
Fatigue	45	Section 6.2
Asthenia	44	Section 6.2
Arthralgia	43	Section 6.1
Guillain-Barre Syndrome	38	Warnings and Precautions
Chills	35	*Not labeled*
Malaise	33	Section 6.1
Myalgia	32	Section 6.1
Immunoglobulin Therapy	31	*Not labeled*

Note: PTs occurring with a frequency >30 reports are shown in above table.

Reviewer comments: Most PTs are labeled events. The unlabeled PT for *Chills* is related to pyrexia (labeled). The unlabeled PT for *Immunoglobulin Therapy* represents a treatment and not a clinical adverse event.

6.2.3 Non-serious Reports

During the reporting period, there were 5,495 non-serious reports; of which 1,196 involved pediatric individuals. 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 July 1, 2022 (Label Section)*
Injection Site Pain	736	Adverse Reactions, Section 6.1
Pain in Extremity	639	Adverse Reactions, Section 6.1
Pain	623	Adverse Reactions, Section 6.1
Pyrexia	531	Section 6.1
Rash	333	Section 6.1
Immunoglobulin Therapy	329	*Not labeled*

Preferred Term (PT)	# Non-serious Reports	*Label Status *Label dated July 1, 2022 (Label Section)*
Nausea	319	Section 6.1
Chills	304	Not labeled
Fatigue	292	Section 6.2
Arthralgia	223	Section 6.1
Malaise	185	Section 6.1

Reviewer comments: Most PTs are labeled events. As mentioned previously, *Immunoglobulin Therapy* represents a treatment and not a clinical adverse event.

6.3 Data mining

Data mining was performed to evaluate whether any reported events following the use of Fluarix 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 November 25, 2022, for INFLUENZA (SEASONAL) (FLUARIX QUADRIVALENT) identified the following PTs (displayed in Table 6) 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).

Table 6: Data mining findings

Preferred Term (PT)	# Reports	*Label Status *Label dated July 1, 2022 (Label Section)*
Shoulder injury related to vaccine administration	33	*Unlabeled*
Product complaint	30	*Unlabeled*
Congenital anomaly	7	*Unlabeled*
Near death experience	13	*Unlabeled*
Product administered at inappropriate site	170	*Unlabeled*

Reviewer comments: Shoulder injury related to vaccine administration may be related to provider technique. PTs for *Product complaint* and *Product administered at inappropriate site* do not represent clinical adverse events. The PT for *congenital anomaly* appeared in 7 reports received from February 2014 to January 2017 (prior to PAC review period).. The reports either describe pregnancy outcomes(e.g., trisomy 18) without evidence of an association with vaccination or indicate the mother had amniocentesis but do not describe an adverse event. Three of the cases were solicited events identified from the sponsor's pregnancy registry, and none of these cases were adjudicated to be due to the vaccine.

Near death experience is a PT that is no longer used by MedDRA; review of the reports often describe vague events, with minimal clinical details, or vaso-vagal syncope.

6.4 Periodic safety reports

The manufacturer's postmarketing periodic safety reports for Fluarix 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 December 6, 2022 for peer-reviewed literature, with the search term "Fluarix Quadrivalent" and "safety" limited by human species, and dates from PAC trigger (January 11, 2018) to date of search, December 6, 2022, retrieved 2 publications pertaining to safety. No new safety concerns for Fluarix QIV were identified in the review of these publications, summarized in the table below:

Publication	Authors' Safety Conclusion
Infect Dis Ther, 2022 Feb;11(1):463-483	The safety profile of 1,000 German and Belgian subjects who received Fluarix Tetra in 2020/21 was reviewed. No safety signals were detected.
Hum Vaccin Immunother. 2020 Aug 2;16(8):1762-1771	A review of 16,000 English subjects who were vaccinated with quadrivalent Influenza vaccines in 2017/18 demonstrated a safety profile consistent with the profile provided by the European Medicines Agency

8 CONCLUSION

This postmarketing pediatric safety review was triggered by the approval of STN 125127/834 on January 11, 2018 to extend the age range for use of Fluarix Quadrivalent to include children 6 to 35 months of age. Review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for Fluarix 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 Fluarix Quadrivalent.