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: Sanofi Pasteur Inc.

Product: Fluzone Quadrivalent (Fluzone QIV)

STN: 103914/6931

Indication(s): Fluzone QIV is a vaccine indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine.

Fluzone QIV is approved for use in persons 6 months of age and older.

Meeting Date: Pediatric Advisory Committee Meeting, April 29 – 30, 2025

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 January 23, 2019, approval of Fluzone quadrivalent (QIV) (Submission Tracking Number 103914/6208) for a new dose presentation (0.5 mL single dose) in individuals 6 to < 36 months of age; of note, Fluzone QIV was already approved for use in individuals 6 months and older (please see regulatory history below).

This memorandum documents the complete evaluation of the Food and Drug Administration (FDA), 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.

1.1 Product Description and Indication

Fluzone QIV (Influenza Vaccine) for intramuscular use is an inactivated influenza vaccine, prepared from influenza viruses propagated in embryonated chicken eggs.

Fluzone QIV is a vaccine indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. Fluzone QIV is approved for use in persons 6 months of age and older.

1.2 Pertinent Regulatory History

- June 7, 2013: STN 103914/5574 approval of Fluzone QIV for use in persons 6 months of age and older.
    - This approval was the trigger for a previous PAC safety and utilization review for the period of June 7, 2013 to June 30, 2015 (please see PAC safety and utilization review memorandum STN 103914/5574).
- January 23, 2019: STN 103914/6208
    - Approval to include a 0.5 mL dose in children 6 to < 36 months of age (i.e., in addition to the 0.25 mL dose for this age group).
    - Regulatory trigger for current PAC review.

2 MATERIALS REVIEWED

- Vaccine Adverse Events Reporting System (VAERS)
    - VAERS reports for Fluzone QIV received during January 23, 2019, to September 30, 2024 (PAC review period)
- Manufacturer's Submissions
    - Fluzone QIV US package insert (updated July 2024)
    - Applicant response to Information Request regarding dose distribution data, received November 21, 2024 (STN 103914/6931)
    - Pharmacovigilance Plan, Version 1.0, dated September 25, 2018
    - Periodic safety reports
- FDA documents
    - STN 103914/6208 Fluzone QIV approval letter dated January 23, 2019
    - STN 103914/6208 Fluzone QIV Pharmacovigilance Plan Review Memorandum
- Publications (see Literature Search in Section 7)

3 LABEL CHANGES IN REVIEW PERIOD

There were no safety related labeling changes during the PAC review period, January 23, 2019, to September 30, 2024

4 PRODUCT UTILIZATION DATA

The manufacturer provided estimates of Fluzone QIV distribution data for the US and worldwide for the PAC review period. The manufacturer estimates that during the PAC review period of January 23, 2019, to September 30, 2024, distribution was as follows:

	Doses distributed		
	US	Other Countries	Total
Pediatric	104,918,890	7,415,033	112,333,923
Adult	114,875,588	74,922,124	189,797,712
All Ages	219,794,478	82,337,157	302,131,635

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. The manufacturer provided these data for FDA review. Distribution data are protected as confidential commercial information and may require redaction from this review.

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan

The manufacturer's current Pharmacovigilance Plan (PVP), Version 1.0, dated September 15, 2018, lists the following important identified risks, important potential risks, and missing information for Fluzone QIV (see Table 1).

Table 1: Fluzone QIV safety concerns

Important identified risks*	Anaphylactic reactions/hypersensitivity
Important potential risks	Guillain-Barré syndrome (GBS) Neuritis Convulsions (including febrile) Encephalomyelitis and transverse myelitis Thrombocytopenia Vasculitis
Missing information	Use during pregnancy Use during breastfeeding Use in patients with hepatic impairment

*The PVP for Fluzone QIV lists anaphylaxis/hypersensitivity as an Important Potential Risk, based on experience with other Fluzone (trivalent) and Fluzone High-Dose (trivalent).

Anaphylactic reactions/hypersensitivity: The Fluzone package insert (PI; July 2024) includes preventing and managing allergic reactions under section 5 Warnings and Precautions, and it lists anaphylaxis and other allergic/hypersensitivity reactions (including urticaria, angioedema) under section 6.2 Postmarketing Experience.

GBS: GBS is labeled under section 5 Warnings and Precautions, section 6.2 Postmarketing Experience, in the Fluzone PI (July 2024).

Myelitis (including encephalomyelitis and transverse myelitis), thrombocytopenia, vasculitis, and neuropathy (including neuritis and brachial plexus neuropathy) are listed under section 6.2 Postmarketing Experience.

The important identified and potential risks listed in Table 1 are monitored with routine pharmacovigilance, including review of adverse event reports submitted to FDA, manufacturer submitted periodic safety reports, published literature, and data mining. Except for the pregnancy registry outlined below, there are no postmarketing requirement or commitment (PMR/PMC) safety studies or a Risk Evaluation and Mitigation Strategy (REMS) for Fluzone QIV.

5.2 Safety-related Postmarketing Studies

The following safety-related postmarketing study was described in the June 7, 2013, approval letter for Fluzone QIV for use in persons 6 months of age and older (STN 103914/5574).

Postmarketing commitment (PMC)

PMC#1: *To establish a pregnancy registry that will enroll women exposed to Fluzone QIV during pregnancy and collect data on their outcomes and newborn health status. Annual reports for this registry will be submitted with the periodic Benefit-Risk Evaluation Report (PBRER) for Fluzone Quadrivalent. When the registry has collected data on the outcomes specified in the protocol for 6 years, Sanofi will submit a final study report. After submission of the registry report, Sanofi will continue enrolling in the registry pending CBER review of the report and determination that the registry can be discontinued.*

Final protocol submission date: August 15, 2013
Study/trial completion date: June 30, 2019
Final Report Submission date: December 31, 2020

Reviewer comment: Sanofi completed the study and submitted the Final Study Report (FSR) on December 31, 2020. The FSR did not identify any safety concerns related to maternal, obstetrical, pregnancy, or neonatal outcomes following exposure to Fluzone QIV.

6 ADVERSE EVENT REVIEW

6.1 Methods

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event reports following use of Fluzone QIV between January 23, 2019, to September 30, 2024 (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 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 reports for Fluzone QIV during the PAC review period are listed in Table 2 below. There were 9,976 US and 97 foreign reports for the review period January 23, 2019, to September 30, 2024.

Table 2: Fluzone QIV VAERS reports during January 23, 2019, to September 30, 2024

Age	U.S. Serious Non-Fatal*	Foreign Serious Non-Fatal*	U.S. Deaths	Foreign Deaths	U.S. Non-Serious	Foreign Non-Serious	U.S. Total Reported	Foreign Total Reported
<18 years	168	6	21	0	3,279	2	3,468	8
≥ 18 years	465	29	32	2	5,332	8	5,829	39
Unknown	39	50	0	0	640	0	679	50
All Ages	672	85	53	2	9,251	10	9,976	97

*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).

6.2.1 Deaths

There were 14 unique pediatric deaths, described in 21 reports, all from the US, during the PAC review period. These deaths were individually reviewed and are summarized below. Review of death reports did not identify patterns suggesting new safety concerns for Fluzone QIV: the frequency of reports resulting in death was low compared to the overall use of this vaccine (as described in section 4 of this memorandum); alternate etiologies were present in many of the cases (see the below narratives), and the causes of death varied with no single predominant cause.

Pediatric deaths

US pediatric death cases (14)

Infection

Seven deaths were due to infections other than influenza (i.e., not vaccine failure), including meningoencephalitis; complications of gastroenteritis; respiratory infection; aspiration and associated infection; *Streptococcus pyogenes* sepsis; and two cases of vaccine-strain measles in immunocompromised individuals.

- 9-month-old boy (premature infant born at 31 weeks gestation) developed meningoencephalitis 1 day after Fluzone QIV. He experienced intracranial hypertension, cerebral edema, and tonsillar herniation, and he died 6 days later. An autopsy was not performed. His past medical history (PMH) included preterm birth, as stated above.

Reviewer comment: Given the history of preterm birth, complex clinical presentation, and lack of autopsy, it is difficult to assess the etiology of meningoencephalitis and a possible relationship with Fluzone QIV vaccination 1 day earlier.

- 1-year-old boy developed fever, vomiting, and hard stools 9 days after vaccination with Fluzone QIV; hepatitis A (HEP A); measles, mumps, and rubella, live attenuated (MMR);

and varicella, live attenuated (VARCEL). The following day, he was found unresponsive and EMS was called. He experienced asystole and apnea in the ambulance; resuscitation attempts were not successful. Per the autopsy report, the cause of death (COD) was complications of gastroenteritis (unknown organism).

Reviewer comment: Fluzone QIV is an inactivated vaccine, and a causal relationship with gastroenteritis 9 days after vaccination is not biologically plausible.

- 3-year-old boy died 6 days after vaccination with Fluzone QIV and inactivated poliomyelitis virus vaccine (IPV) (and 12 days after HEP A and tetanus toxoid, diphtheria toxoid, and acellular pertussis vaccine, adsorbed; DTaP). Per the autopsy report, the COD was upper respiratory infection, probably of viral origin, with tracheal edema, slight pulmonary consolidation bilaterally, pulmonary lymphadenopathy and histologic inflammatory changes. Results were negative for respiratory viruses.

Reviewer comment: Fluzone QIV is an inactivated vaccine, and a causal relationship with a respiratory infection is not biologically plausible, particularly in the setting of negative test results for respiratory viruses (i.e., this was not a case of influenza vaccine failure).

- 7-month-old boy with a PMH of recent sinusitis died 3 days after Fluzone QIV. Per the autopsy report, the COD was probable aspiration, contributing COD adenovirus, respiratory syncytial virus A, and human rhinovirus detected.

Reviewer comment: Aspiration and infection with adenovirus, RSV, and rhinovirus are not plausibly associated with Fluzone QIV vaccination.

- 6-year-old girl developed fever, emesis, hematuria, pancytopenia, pulmonary hemorrhage, possible disseminated intravascular coagulation, and respiratory arrest 6 days after Fluzone QIV. Resuscitation attempts were not successful. This patient had a PMH of vascular malformation of the lower extremity, recent pharyngitis. The death certificate noted: pulmonary hemorrhage, *Streptococcus pyogenes* bacteremia.

Reviewer comment: This girl appears to have died as a result of bacterial infection/sepsis and its complications, including consumptive coagulopathy. Her death does not appear to be related to Fluzone QIV.

- 17-year-old girl who had a 7-year history of "lumps" in her neck (not evaluated) and who had recently arrived in the US received the following vaccines: Fluzone QIV; hepatitis B (HEP B); HEP A; IPV; human papillomavirus 9-valent; meningococcal quadrivalent conjugate; MMR; tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine, adsorbed; and VARCEL. Eight days after vaccination, excisional biopsy of cervical lymph nodes revealed Hodgkin's lymphoma (nodular sclerosis). The patient received antineoplastics and the cancer was in remission, but she developed measles pneumonia and died approximately 4 months after vaccination. Autopsy and viral genotyping confirmed disseminated measles (vaccine strain).

Reviewer comment: This girl's lymphoma likely preceded vaccination. In immunocompromised individuals, the risk of viral dissemination following a live attenuated vaccine is well known. This death does not appear to be related to Fluzone QIV.

- 1-year-old boy with hepatoblastoma developed pulmonary nodules and pneumonia approximately 2 months after vaccination with Fluzone QIV, HEP A, MMR, and VARCEL. Approximately 3 months later (5 months after vaccination), he was diagnosed with measles (vaccine strain) complicated by hemophagocytic lymphohistiocytosis and multiorgan failure, and he died. The patient's PMH also included vaccine-associated varicella.

Reviewer comment: In immunocompromised individuals, the risk of viral dissemination following a live attenuated vaccine is well known. This death does not appear to be related to Fluzone QIV.

Unexplained / undetermined cause of death

There were four unexplained deaths, including three with autopsies: two were sudden unexplained death in childhood and one was undetermined cause of death; without an autopsy, the fourth case is difficult to assess (please see comments below).

- 13-month-old boy died ~18 hours after Fluzone QIV (and 22 days after MMR and *Haemophilus influenzae type* b conjugate vaccine; HIBV). Per the autopsy report, the COD was sudden unexpected death in epilepsy. His PMH included covid-19 and seizures.

Reviewer comment: The Institute of Medicine has rejected a causal relationship between multiple simultaneous vaccines and sudden infant death syndrome (SIDS) (IOM/ISRC, 2003). Approximately four million children are born in the US each year, and infants receive ≥15 immunizations on 4-5 occasions in the first 12 months of life. About 1/1500 babies dies of SIDS in the US each year. Therefore, 50-100 babies each year can be expected to die of SIDS within 2 days of vaccination, purely as a matter of chance. In addition, the history of epilepsy may have placed the boy at risk for a seizure event.

- 2-year-old girl died 7 weeks after Fluzone QIV. She was found unresponsive with vomitus next to her; postmortem respiratory panel was positive for coronavirus and rhino- or enterovirus, but gross and microscopic examination did not reveal evidence of viral infection. Bacterial blood cultures and toxicology panel were negative. The autopsy report indicated the cause of death (COD) as sudden unexpected death in childhood, manner of death is natural.

Reviewer comment: Death occurred 7 weeks after vaccination, with no evidence of trauma, life-threatening congenital malformation, or infectious disease. The interval from vaccination to death makes a causal association unlikely.

- 13-month-old girl found unresponsive on sofa 2 days after vaccination with Fluzone QIV, HEP B, pneumococcal 13-valent (PCV13), and Pentacel. The autopsy report indicated undetermined cause and manner of death; there were small circular subgalaeal hemorrhages (right occipital, bitemporal, and frontal); underlying skull and brain intact. Viral polymerase chain reaction was negative; bacterial culture of lungs grew multiple organisms consistent with artifact of postmortem interval. She had a past medical history (PMH) of apneic episode at age 4 months (not evaluated).

Reviewer comment: As stated above, 50-100 children each year may die of sudden death within days following vaccination, as a matter of chance. This case is also notable for an atypical sleeping environment and history of apneic episode.

- 5-year-old boy experienced syncope 19 days after Fluzone QIV. After the syncopal episode, he was tired and slightly confused but returned to his normal self the same day. Throughout the night, the patient's father checked him every 2 hours, and the boy was reportedly fine. The following morning, he was noted to be choking on secretions and had no pulse. His mother performed CPR, and his parents brought him to the emergency department. The team administered CPR for over an hour but resuscitation attempts were not successful. The patient's parents did not want any testing, but MD requested evaluations for cardiomyopathy and channellopathy; His PMH included atopic dermatitis, wheezing, speech delay, seasonal allergic rhinitis, sensory disorder, and croup.

Reviewer comment: Syncope 19 days after vaccination is not consistent with a vasovagal response, anaphylaxis, or other immediate vaccine-related effect. The boy was reportedly fine that evening. Without an autopsy, it is difficult to assess the etiology of his choking/dyspnea and cardiac arrest, and the limited information precludes assessment of causal relationship with Fluzone QIV vaccination 20 days earlier.

Abdominal compartment syndrome and perforated viscus

- 2-year-old girl developed vomiting, abdominal distension, respiratory distress, and pulseless electrical activity 6 days after Fluzone QIV. An emergency laparotomy and decompression revealed abdominal compartment syndrome, perforated viscus, and purulent material; no evidence of bowel ischemia/infarction or malrotation. Resuscitation attempts were not successful. No autopsy report or death certificate is available. Per the operative report: *"There was a significant amount of purulent material coming from the pelvis. The bowel was healthy and pink with no evidence of malrotation and no evidence of ischemia. The Emergency Department team and the Pediatric Intensive Care Unit team continued the PALS [pediatric advanced live saving] algorithm for cardiac arrest…. I continued at the bedside throughout the PALS response until the child was declared deceased by the PICU physician after multiple rounds of CPR with epinephrine, as well as IV fluid resuscitation and O-negative blood transfusion."*

Reviewer comment: This girl experienced signs and symptoms of an acute abdomen / bowel perforation, and unfortunately surgical intervention was too late. As an intramuscular, inactivated vaccine, Fluzone QIV is unlikely to cause an intraluminal process or peri-intestinal lymphadenopathy that could precipitate bowel obstruction/perforation.

Intestinal ischemia due to congenital intra-abdominal adhesion band

- 1925073: 1-year-old boy experienced vomiting, oliguria, and lethargy 14 days after vaccination with Fluzone QIV, HIBV, PCV13, and VARCEL. He presented to a community hospital and was found to have metabolic acidosis. He was transferred to a university hospital for a higher level of care and may have had a seizure in the ambulance. Upon arrival at the university hospital, he was unresponsive and became pulseless. Resuscitation attempts were not successful. Per the autopsy report, the COD was ketoacidosis due to intestinal ischemia due to congenital intra-abdominal adhesion band. His PMH included laryngotracheomalacia, GERD, and a recent upper respiratory infection.

Reviewer comment: This boy died of complications related to a congenital anomaly. His death does not appear to be related to Fluzone QIV.

Accidental asphyxia

- 2687127: 12-month-old girl died 1 day after Fluzone QIV, HEPA, MMR, and PCV13. Per the autopsy report, the COD was probable asphyxia in atypical sleeping environment. Bedding material was covering her face, and her sibling had joined her in the crib, unbeknownst to their parents). There was evidence of injury, including contusions of forehead, nose, and left foot, subgaleal hemorrhage, abrasions of left ear, back, and left thigh. Respiratory cultures were positive for enterovirus. The manner of death was noted to be accidental.

Reviewer comment: Per the autopsy report, the atypical sleeping environment and bruises suggest that the girl was unable to reposition herself and therefore died of accidental asphyxia. Her death does not appear to be related to Fluzone QIV.

Foreign pediatric death reports (0)

Adult death reports

During the PAC review period, there were 34 death reports pertaining to adults (32 US and 2 foreign). Median age was 62.5 years (range 21-91), with 14 females and 20 males. Median onset to earliest sign/symptom was 7 days (range 0-496) with two missing values. The most common PTs were *asthenia* (n=8), *cardiac arrest* (n=7), *dyspnea* (n=7), *endotracheal intubation* (n=7), and *unresponsive to stimuli* (n=7). For cases for which medical records, autopsy reports, and/or death certificates were available, manual review revealed that deaths were related to typical diagnoses in this age group, e.g., cardiovascular disease and COVID-19.

Reviewer comment: These results do not raise any new concerns about the safety of Fluzone QIV.

6.2.2 Serious Reports

During the PAC review period, there were 757 serious non-fatal reports, including 174 pediatric reports and 494 adult reports. Age was unknown for the remaining 89 reports.

The most common Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) for pediatric serious 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 serious reports in individuals < 18 years

Preferred Term (PT)	**# Serious Reports**	**Label Status** *Fluzone PI updated July 1, 2024*
Pyrexia	62	labeled
Vomiting	45	labeled
Seizure	29	related to labeled event
Tachycardia	25	related to labeled event
Irritability	24	labeled
Unresponsive to stimuli	24	labeled
Cough	22	related to labeled event
Gait disturbance	21	related to labeled event
Intensive care	20	related to labeled event
Diarrhoea	19	not labeled
Death	19	not labeled
Headache	18	labeled
Rash	18	related to labeled event
Fatigue	17	labeled
Immunoglobulin therapy	17	related to labeled event
Lethargy	17	related to labeled event
Injection site pain	16	labeled
Tremor	15	related to labeled event
Febrile convulsion	15	labeled
Nausea	15	related to labeled event

Note: PTs occurring with a frequency >14 reports are shown in above table.

Reviewer comment: Most PTs are labeled events or related to labeled events. The unlabeled PT of *Intensive care* is non-specific and describes a variety of underlying conditions, such as myocarditis associated with COVID-19 vaccine, encephalitis, and congenital anomalies. Reports of *immunoglobulin therapy* most commonly pertain to cases of GBS or immune thrombocytopenia. Reports of *seizure* describe convulsive syncope or seizures (unspecified). *Gait disturbance* is most commonly associated with injection site reactions after lower extremity vaccination in infants/toddlers. The unlabeled PT for *diarrhea* is non-specific and may represent infectious etiologies. Review of cases did not reveal any unusual patterns and no new safety concerns were identified.

The most common PTs overall (i.e., all ages) for serious 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 serious reports (all ages)

Preferred Term (PT)	**# Serious Reports**	**Label Status** *Fluzone PI updated July 1, 2024*
Pyrexia	135	labeled
Pain	114	labeled
Asthenia	95	labeled
Pain in extremity	93	labeled
Hypoaesthesia	91	related to labeled event
Headache	89	labeled
Vomiting	85	labeled
Muscular weakness	83	related to labeled event
Fatigue	80	labeled
Dyspnea	80	labeled
Paraesthesia	79	labeled
Nausea	74	related to labeled event
Guillain-Barré syndrome	74	labeled
Condition aggravated	69	related to labeled event
Gait disturbance	67	related to labeled event
Cough	61	labeled
Immunoglobulin therapy	61	related to labeled event
Intensive care	61	related to labeled event
Dizziness	60	labeled
Arthralgia	58	related to labeled event

Note: PTs occurring with a frequency >57 reports are shown in above table.

Reviewer comment: These events are already known and labeled (or related to a labeled term). Although not shown in the memo, the entire list of PTs appearing in serious reports was assessed, and no unusual or unanticipated patterns were noted. For reports of *muscular weakness, immunoglobulin therapy,* and *intensive care,* GBS is the most common diagnosis accounting for these PTs.

6.2.3 Non-serious Reports

During the reporting period, there were 9,261 non-serious reports, of which 3,281 involved individuals younger than 18 years. Table 5 below lists the 20 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: Most frequently reported PTs in non-serious reports (all ages)

Preferred Term (PT)	**# Non-serious Reports**	**Label Status** *Fluzone PI updated July 1, 2024*
No adverse event	1,442	not an adverse event
Pain	834	labeled
Injection site erythema	769	labeled
Injection site pain	745	labeled
Pain in extremity	742	labeled
Pyrexia	739	labeled
Injection site swelling	636	labeled
Dizziness	568	labeled
Product storage error	556	not an adverse event
Erythema	512	labeled
Headache	508	labeled
Rash	465	related to labeled event
Urticaria	438	labeled
Fatigue	431	labeled
Expired product administered	420	not an adverse event
Nausea	404	related to labeled event
Pruritus	384	labeled
Extra dose administered	382	not an adverse event
Syncope	378	labeled
Wrong product administered	369	not an adverse event

Reviewer comment: Most of these events are already known and labeled, or they are not adverse events. There was substantial overlap among reports with PTs of *no adverse event, expired product administered, extra dose administered, product storage error,* and *wrong product administered.* Some reports described confusion of one influenza vaccine for another, or errors that occurred with other vaccines which were administered to the patient on the same day (e.g., covid, Tdap, hepatitis B, MMR, and respiratory syncytial virus). Reports of *product storage error* primarily pertained to temperature excursions outside the range listed in the PI (2° to 8°C). Among reports of *wrong product administered* with no concomitant vaccines, the most common error was confusion of Fluzone Quadrivalent and Fluzone High-Dose Quadrivalent. Please see additional comments below.

6.3 Data mining

Data mining was performed to evaluate whether any reported events following the use of Fluzone 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 29, 2024 for INFLUENZA (SEASONAL) (FLUZONE QIV) 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** *Fluzone PI updated July 1, 2024*
Wrong product administered	487	not an adverse event
Underdose	298	not an adverse event
Guillain-Barré syndrome	161	labeled
Incorrect dose administered	154	not an adverse event
Medication error	150	not an adverse event
Poor quality product administered	122	not an adverse event
Syringe issue	108	not an adverse event
Exposure via skin contact	50	not an adverse event
Needle issue	36	not an adverse event
Product distribution issue	31	not an adverse event

<u>*Reviewer comment*</u>: Most of these terms are not adverse events. Regarding *wrong product administered,* please see above. Of reports with a PT of *underdose,* only 24 pertained to confusion of the 0.25-mL and 0.5-mL doses of Fluzone Quadrivalent; all of these reports were non-serious and did not involve an AE. Other reports of *underdose* and *incorrect dose administered* pertained to covid vaccinations administered on the same day (e.g., confusion of pediatric vs adult dose of covid vaccine), or sudden patient movement that resulted in the needle slipping out before the full dose of vaccine was administered. The latter was also associated with *exposure via skin contact.* Reports with a PT of *poor quality product administered* described temperature excursions and shipment delays. Of the reports of medication errors, fewer than 10% described any AEs; of the errors that were associated with an AE, injection site reactions and other local signs/symptoms were the most common.

GBS is labeled under section 5 Warnings and Precautions, section 6.2 Postmarketing Experience, in the current Fluzone PI (July 1, 2024).

6.4 Periodic safety reports

The manufacturer's postmarketing periodic safety reports for Fluzone 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 4, 2024, for peer-reviewed literature, with the search term "Fluzone QIV" and "safety" limited by human species, and publication dates from PAC trigger (January 23, 2019) to September 30, 2024, retrieved 5 publications pertaining to safety. No new safety concerns for Fluzone QIV were identified in the review of these publications, summarized in the table below:

Publication	**Authors' Safety Conclusion**
Betancourt-Cravioto et al. Improved post-marketing safety surveillance of quadrivalent inactivated influenza vaccine in Mexico using a computerized, SMS-based follow-up system. Hum Vaccin Immunother. 2022 Dec 31;18(1):1935170. doi: 10.1080/21645515.2021.1935170. Epub 2021 Aug 18. PMID: 34406896; PMCID: PMC8920169.	active surveillance system monitoring nine sites across three influenza seasons; no new safety concerns
Ledlie et al. Exposure to quadrivalent influenza vaccine during pregnancy: Results from a global pregnancy registry. Influenza Other Respir Viruses. 2022 Jan;16(1):90-100. doi: 10.1111/irv.12897. Epub 2021 Sep 14. PMID: 34520127; PMCID: PMC8692812.	the manufacturer summarized 229 vaccine exposures during pregnancy; more than 85% full-term births; four congenital anomalies; no new safety concerns
Statler et al. Immunogenicity and safety of a quadrivalent inactivated influenza vaccine in children 6-59 months of age: A phase 3, randomized, noninferiority study. Vaccine. 2019 Jan 7;37(2):343-351. doi: 10.1016/j.vaccine.2018.07.036. Epub 2018 Jul 26. PMID: 30057283.	randomized, age-stratified study of non-inferiority of Afluria QIV compared with Fluzone QIV; no new safety concerns
Agarkhedkar et al. Immunogenicity and safety of an intramuscular split-virion quadrivalent inactivated influenza vaccine in individuals aged ≥ 6 months in India. Hum Vaccin Immunother. 2019;15(4):973-977. doi: 10.1080/21645515.2019.1565259. Epub 2019 Mar 12. PMID: 30762467; PMCID: PMC6605869.	open-label multicenter trial to evaluate safety and immunogenicity in children, adolescents, and adults; no new safety concerns
Montalban et al. Immunogenicity and safety of the 2015 Southern Hemisphere formulation of a split-virion inactivated quadrivalent vaccine. Hum Vaccin Immunother. 2018 Mar 4;14(3):593-595. doi: 10.1080/21645515.2017.1377378. Epub 2017 Oct 30. PMID: 28933626; PMCID: PMC5861779.	Open-label postmarketing trial to confirm safety and immunogenicity in adults; no new safety concerns

8 CONCLUSION

This postmarketing pediatric safety review was triggered by the approval of January 23, 2019, approval of STN 103914/6208 to include the use of a 0.5 mL single dose presentation of Fluzone QIV formulation in children 6 to < 36 months of age. Review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for Fluzone 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 continuing routine safety monitoring of Fluzone QIV.