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

MEMORANDUM

To:	Christopher Jankosky, MD, MPH Acting Director, Division of Epidemiology (DE), Office of Biostatistics and Epidemiology (OBE), Center for Biologics Evaluation and Research (CBER)
Through:	Craig Zinderman, MD, MPH Associate Director of Product Safety, DE, OBE, CBER Meghna Alimchandani, MD Acting Branch Chief, OBE/DE/PVB
From:	David Menschik, MD, MPH Medical Epidemiologist, OBE/DE/PVB
Subject	Fluzone Quadrivalent Pediatric Safety and Utilization Review for the Pediatric Advisory Committee (PAC)
Sponsor:	Sanofi Pasteur
Product:	Fluzone Quadrivalent (Influenza Virus Vaccine)
STN:	103914/5574
Indication:	For active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. Fluzone Quadrivalent is approved for use in persons 6 months of age and older.
Meeting Date:	Pediatric Advisory Committee Meeting, April 12, 2016

1. Introduction

1.1 Trivalent vs. Quadrivalent Formulations of Seasonal Influenza Vaccines

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.

1.2 Regulatory History

1.2.1 Fluzone (trivalent formulation)

Fluzone was initially approved in the US in 1980. Fluzone is indicated for active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccines. Fluzone is approved for use in persons 6 months of age and older.

1.2.2 Fluzone Quadrivalent

Fluzone Quadrivalent (Fluzone QIV) is an inactivated quadrivalent influenza virus 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. Fluzone QIV was approved in the US on June 7, 2013. Fluzone QIV is approved for use in persons 6 months of age and older.

The processes for manufacturing this quadrivalent influenza vaccine are similar to those for the Fluzone (trivalent) vaccine, aside from the addition of a B strain at the formulation step. The hemagglutinin (HA) antigen concentration per 0.5 mL dose is 15 μg HA per strain, the same as for the trivalent product. Thus, each dose of Fluzone QIV contains a total of 60 μg HA, rather than 45 μg HA in the trivalent formulation. 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.[1]

2. Objective

The objective of this memorandum for the Pediatric Advisory Committee (PAC) is to present a comprehensive review of the postmarketing pediatric safety covering a period including 18 months following the initial licensure 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 is the June 7, 2013 approval of Fluzone Quadrivalent for use in persons 6 months and older. This review covers the period

from the date of approval through June 30, 2015, spanning two annual influenza seasons.

An abbreviated presentation of this review to the PAC is planned for this product as it does not meet the criteria that would necessitate a full oral presentation or a justified abbreviated presentation. Specifically, no new safety signals were identified. During the review period, there were no reports of pediatric deaths that were attributed to Fluzone QIV. While four pediatric deaths were reported in the review period, they were not attributed to Fluzone QIV due to documentation of alternate causes of death when available (e.g., from autopsy reports), and based on careful FDA medical/epidemiological review of each case. The product does not have a requirement for a post-marketing study or Risk Evaluation and Mitigation Strategy (REMS), and there have been no label changes regarding safety. Although the PAC presentation is abbreviated, the analysis of the safety data is comprehensive, and this memorandum documents FDA's full and complete evaluation, including review of adverse event reports in passive surveillance data, periodic safety reports from the manufacturer, data mining, and a review of the published literature.

3. Materials Reviewed

3.1 Vaccine Adverse Events Reporting System (VAERS)

VAERS reports for Fluzone QIV (June 7, 2013 – June 30, 2015)

3.2 Manufacturer's Submissions

- Fluzone Quadrivalent US package insert, dated February 2014
- Letters regarding dose distribution data, dated September 9, 2015 and November 3, 2015
- Risk Management Plan, dated February 12, 2012
- Pregnancy registry protocol, dated June 26, 2012
- Periodic Benefit-Risk Evaluation Reports from licensure through September 14, 2014

3.3 FDA Documents

Fluzone Quadrivalent Approval Letter, dated June 7, 2013

3.4 Publications (see end notes)

4. Label changes in review period

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

5. Product utilization data

According to the manufacturer, 46,127,640 doses of Fluzone QIV were distributed in the US from June 7, 2013 to June 30, 2015. Among these distributed doses, the

manufacturer reports that 11,924,570 were 0.25 mL pre-filled syringes, intended for use in individuals 6 months through 35 months of age. No further data is available regarding age specific utilization. The number of doses distributed is an estimate of the number of vaccinations administered, particularly since individuals may receive more than one dose and doses may have been distributed without being administered to patients.

6. Pharmacovigilance

From pre-licensure clinical studies, there were no important identified risks for Fluzone QIV. During the postmarketing review period there have been no new identified risks. As Fluzone QIV is manufactured using the same process as for Fluzone (trivalent formulation), the adverse events of special interest (AESI) considered potential risks for Fluzone were considered as potential risks for Fluzone QIV as well. These AESIs, which are to be evaluated and reported in periodic safety update reports, were: anaphylaxis and other allergic/hypersensitivity reactions (including urticaria, angioedema), convulsions (including febrile), facial palsy (Bell's palsy), Guillain-Barré syndrome, myelitis (including encephalomyelitis and transverse myelitis), optic neuritis/neuropathy, syncope (shortly after vaccination), Stevens-Johnson syndrome, thrombocytopenia, and vasculitis. There have been no postmarketing signals for these AESIs after Fluzone QIV to date.

A pregnancy registry was established on August 16, 2013 intended to collect and analyze information on vaccine exposures, pregnancy outcomes, and fetal/offspring outcomes. Through the most recent annual PBRER (Periodic Benefit-Risk Evaluation Report; data lock point September 15, 2014), there were four pregnancy cases captured, with outcome statuses unknown for three cases and the remaining case outcome was a live birth with no congenital anomalies. Per postmarketing commitment stated in the approval letter, annual reports for this registry will be submitted via PBRER with a final study report to be submitted by December 31, 2020. Enrollment will continue after submission of the final study report until FDA review and determination that the registry can be discontinued.

There are no other completed or outstanding postmarketing safety study commitments or requirements for Fluzone QIV. The sponsor's PBRERs do not suggest any change in Fluzone QIV's overall benefit-risk profile. The sponsor has not identified any new safety signals, nor any risks or potential risks that were not already identified at the time of approval. As the sponsor states, this product's benefit-risk balance remains unchanged for the approved indication based on available data.

7. Vaccine Adverse Event Reporting System

7.1 Methods

The Vaccine Adverse Event Reporting System (VAERS) was queried for events following use of Fluzone QIV reported from June 7, 2013 through June 30, 2015. Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, variable quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups.

7.2 Results

The table below summarizes VAERS Fluzone QIV reports received during the review period.

Table 1. VAERS Reports for Fluzone Quadrivalent (June 7, 2013 through June 30, 2015)

	Serious* Non-Fatal (includes OMIC)		Deaths		Non-serious		Total	
Age	US	Foreign	US	Foreign	US	Foreign	US	Foreign
<3 years	15	0	4	0	127	0	146	0
3-17 years	20	0	0	0	178	0	198	0
≥18 years	51	0	3	0	630	0	675	0
Unknown	0	0	0	0	9	0	9	0
Total	86	0	7	0	944	0	1028	0

*Serious adverse events (including OMIC; Other Medically Important Conditions) are defined in 21 CFR 600.80.

7.2.1 Deaths

During the reporting period there were 4 deaths in individuals <18 years old and 3 deaths in individuals ≥ 18 years old. No deaths were attributed to vaccination with Fluzone QIV.

Synopses of these fatal cases follow (with causes of death specified from autopsy when available):

Pediatric deaths:

- A 2 year-old male with a medical history including multiple congenital cardiac anomalies (hypoplastic right heart, tricuspid atresia, pulmonary hypertension, VSD, ASD, bicuspid aortic valve and aortic stenosis), bronchiolitis, and chronic cyanosis, experienced respiratory distress four days after Fluzone QIV receipt progressing to cardiopulmonary arrest. Per autopsy report, he died from an acute exacerbation of reactive airway disease due to an Enterovirus respiratory infection.
- A 20 month-old female was discovered unresponsive in her bed, face down in emesis the day after multiple vaccinations including Fluzone QIV, DTaP, Hepatitis A, and PCV13 vaccines. Autopsy revealed food lodged in larynx and trachea consistent with aspiration and airway obstruction. Per autopsy report, the immediate cause of death was asphyxia.

- A 13 month-old male was found unresponsive in his bumper-padded crib the morning after receiving Fluzone QIV and after recent administration of ibuprofen and acetaminophen for teething. He had underlying gastroesophageal reflux disease for which he was receiving daily ranitidine. He had been seen nine days prior at his pediatrician's office due to cough and cold symptoms for two days and had been diagnosed with an upper respiratory infection. He had received Hepatitis A, MMR, PCV13, and varicella vaccines about a month earlier. Per autopsy report, he died of undetermined causes.
- A 14 month-old male was found lying face down and unresponsive in his crib eight days after multiple vaccinations including Fluzone QIV, HIB, and PCV13 vaccines. He had been taking acetaminophen for fever. Per autopsy report, he died of sudden unexpected death in childhood.

Adult deaths:

- A 59 year-old female died of septic shock due to pneumococcal bacteremia thirteen days after receiving Fluzone QIV.
- A 25 year-old male died of multiple organ failure secondary to acute gastrointestinal hemorrhage per autopsy two days after receiving Fluzone QIV.
- A 74 year-old died from cardiogenic shock due to myocardial infarction approximately two and a half months after receiving Fluzone QIV.

7.2.2 Serious reports

During the reporting period, there were 94 serious (including fatal and OMIC) reports, 39 of which involved individuals <18 years old. Of these 39 reports, there were two pairs of duplicate reports yielding 37 serious cases which are summarized in the following table.

Table 2. Serious VAERS Reports for Fluzone Quadrivalent (6/7/13 – 6/30/15; <18 years old)

Principal Adverse Event*	n = 37
Local reactions	
Injection site reaction or cellulitis	6
Nervous system conditions	
Febrile Seizure	5
Guillain-Barré syndrome	3
Seizure recurrence (pre-existing epilepsy)	2
Acute transient tic disorder	1
Afebrile seizure (new onset)	1
Posturing	1
General signs, symptoms, conditions	
Sudden unexpected death <2 years old (after autopsy)	2
Acute life threatening event	1
Asphyxia due to aspiration	1
Fever of unknown origin	1
Vomiting and dehydration	1
Lethargy	1
Immunologic disorders	
Allergic/hypersensitivity reaction	2
Kawasaki disease	1
Respiratory conditions	

Reactive airway disease exacerbation	1
Upper respiratory infection	1
Hematologic condition	
Pancytopenia	1
Idiopathic thrombocytopenic purpura	1
Gastrointestinal conditions	
Gastritis	1
Intussusception	1
Urinary/renal disorder	
Hematuria with cystitis	1
Nephrotic syndrome	1

* Based on review of the reported signs, symptoms, and diagnoses, the most important clinical entity was determined to be the principal adverse event.

7.2.3 Non-serious reports

During the reporting period, there were 944 non-serious reports, 305 of which involved individuals <18 years old. Most non-serious reports were consistent with the known safety profile of influenza vaccines. In this pediatric group, the most commonly reported (n≥100) non-serious adverse event MedDRA preferred terms (PTs) were: injection site erythema (n=170), pyrexia (n=163), injection site pain (n=119), injection site swelling (n=116), pain (n=109), and erythema (n= 102).

7.3 Data Mining

Data mining was conducted to evaluate whether any 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. Data mining findings are subject to a number of potential limitations and do not imply causality. 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 on July 21, 2015 (data recent as of July 20, 2015) revealed no statistical signals of disproportionate reporting for Fluzone QIV (2013-14); disproportional reporting alerts were identified for Fluzone QIV (2014-2015) for the following adverse event PTs[1]:

- *Incorrect dose administered* (n=20)

  The association with this PT is being driven by a cluster of 20 reports submitted within 3 days of each other from the same institution, describing 20 instances of an underdose with no adverse event reported.
- *Underdose* (n=17)

  The association with this PT is being driven by a cluster of 17 reports submitted with 11 days of each other from the same institution, describing 17 instances of an underdose with no adverse event reported.

8. Literature review

A search of the US National Library of Medicine's PubMed.gov database for peer-reviewed literature conducted on September 28, 2015 using the search term "Fluzone"

[1] "2013-14" refers to vaccinations given between July 1, 2013 and June 30, 2014 and "2014-15" refers to vaccinations given between July 1, 2014 and June 30, 2015.

published between June 7, 2013 and June 30, 2015, yielded no publications with any new potential safety signal for Fluzone QIV.

9. Safety surveillance for influenza vaccines

During each Northern Hemisphere influenza season, the FDA, CDC, and CMS collaborate and share information generated through several surveillance systems. In aggregate, these systems facilitate three key components of influenza vaccine safety surveillance: safety signal detection, surveillance for pre-specified adverse events of interest, and safety signal evaluation.

Safety Signal Detection

Co-managed by the CDC and FDA, VAERS is a spontaneous reporting system that allows healthcare providers, patients, vaccine manufacturers and others to report adverse events suspected to be associated with vaccines, including influenza vaccines.[2] VAERS can assess early indicators of a possible vaccine safety problem that present as new or unusual adverse events or patterns of reports.[3]

FDA and CDC medical officers and epidemiologists routinely review VAERS reports, and the VAERS contractor obtains follow-up information including relevant medical records for further evaluation of serious reported events.[4] Data mining algorithms complement review of VAERS records by identifying adverse events that are disproportionally reported for a particular vaccine compared to other licensed vaccines.[5] New safety signals for influenza vaccines identified through VAERS can be evaluated by methods including case series analyses and controlled epidemiologic studies for safety signal evaluation.

Surveillance for Pre-specified Adverse Events of Interest

Each season, both FDA and CDC use electronic healthcare data to monitor pre-specified adverse events of special interest. Established in 1990, the Vaccine Safety Datalink (VSD) is a collaborative project between the CDC and 9 health care organizations. Weekly VSD Rapid Cycle Analysis enables rate-based comparisons among a population exceeding 9 million individuals. This surveillance usually includes approximately 4-5 adverse events each flu season and involves live and inactivated vaccines.[6,7]

Since 2009, FDA and the Centers for Medicare and Medicaid Services (CMS) have used healthcare claims data for U.S. Medicare beneficiaries to monitor hospitalizations and diagnosis codes for Guillain-Barré Syndrome (GBS) after live and inactivated influenza vaccines. This prospective active adverse event surveillance provides timely GBS rate-based comparisons among a population exceeding 42 million individuals.

Safety Signal Evaluation

In addition to seasonal surveillance for pre-specified adverse events of interest, VSD[8] and CMS[9] databases have been used to evaluate safety signals for flu vaccines. The Post-Licensure Rapid Immunization Safety Monitoring system (PRISM), a

component of the FDA's Sentinel Initiative dedicated to vaccines, has also been used to evaluate safety signals for flu vaccines.[10] The PRISM system uses the FDA's Sentinel Distributed Database which includes a population exceeding 100 million. If warranted, FDA and/or CDC can use such large data sources to evaluate potential safety signals through controlled epidemiologic studies. These studies can determine if an observed safety signal reflects a true association between the influenza vaccine and the adverse event, and if so, ascertain the magnitude of the association.

10. Conclusion

This comprehensive postmarketing pediatric safety review of passive surveillance adverse event reports (including data mining), Periodic Benefit-Risk Evaluation Reports and the published literature does not indicate any new safety concerns for Fluzone QIV since its licensure. There were relatively few reports of adverse events received during the time period of this review, compared to the number of patients expected to have received the vaccine based on dose distribution data. Most adverse event reports were non-serious and were consistent with the known safety profile of influenza vaccines. No unusual frequency, clusters, or other trends were identified that would suggest a new safety concern. The Fluzone QIV package insert adequately reflects the known safety profile for this product.

11. Recommendations

FDA recommends continued routine safety monitoring of Fluzone QIV. No further regulatory action is indicated at this time.

---

[1] CDC. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP) — United States, 2014–15 Influenza Season. Groshkopf LA, Olsen SJ, Skolow LZ, Bresee JS, Cox NJ, Broder KR, Karron RA, Walter EB. Morbidity and Mortality Weekly Report. August 15, 2014. 63(32);691-697.
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6332a3.htm; accessed 9/28/2015

[2] Varricchio F, Iskander J, Destefano F, Ball R, Pless R, Braun MM, Chen RT.. Understanding vaccine safety information from the Vaccine Adverse Event Reporting System. Pediatric Infectious Disease2004 Apr;23(4):287-94.

[3] Salmon DA, Akhtar A, Mergler MJ, Vannice KS, Izurieta H, Ball R, Lee GM, Vellozzi C, Garman P, Cunningham F, Gellin B, Koh H, Lurie N; H1N1 Working Group of Federal Immunization Safety Task Force. Influenza Vaccination Program Immunization-Safety Monitoring Systems for the 2009 H1N1 Monovalent Influenza Vaccination Program. Pediatrics. 2011 May;127 Suppl 1:S78-86.

[4] CDC. Vaccine Adverse Event Reporting System (VAERS)
http://www.cdc.gov/vaccinesafety/Activities/vaers.html; accessed 9/28/2015

[5] Martin D, Menschik D, Bryant-Genevier M, Ball R. Data mining for prospective early detection of safety signals in the Vaccine Adverse Event Reporting System (VAERS): a case study of febrile seizures after a 2010-2011 seasonal influenza virus vaccine. Drug Saf. 2013 Jul;36(7):547-56.

[6] McNeil MM, Gee J, Weintraub ES, Belongia EA, Lee GM, Glanz JM, Nordin JD, Klein NP, Baxter R, Naleway AL, Jackson LA, Omer SB, Jacobsen SJ, DeStefano F. The Vaccine Safety Datalink: successes and challenges monitoring vaccine safety. Vaccine. 2014 Sep 22;32(42):5390-8.

[7] Kawai AT, Li L, Kulldorff M, Vellozzi C, Weintraub E, Baxter R, Belongia EA, Daley MF, Jacobsen SJ, Naleway A, Nordin JD, Lee GM. Absence of associations between influenza vaccines and increased risks of seizures, Guillain-Barré syndrome, encephalitis, or anaphylaxis in the 2012-2013 season. Pharmacoepidemiol Drug Saf. 2014 May;23(5):548-53.

[8] Tse A, Tseng HF, Greene SK, Vellozzi C, Lee GM; VSD Rapid Cycle Analysis Influenza Working Group. Signal identification and evaluation for risk of febrile seizures in children following trivalent

inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010-2011. Vaccine. 2012 Mar 2;30(11):2024-31

[9] Polakowski LL, Sandhu SK, Martin DB, Ball R, Macurdy TE, Franks RL, Gibbs JM, Kropp GF, Avagyan A, Kelman JA, Worrall CM, Sun G, Kliman RE, Burwen DR. Chart-confirmed Guillain-Barré syndrome after 2009 H1N1 influenza vaccination among the Medicare population, 2009-2010. Am J Epidemiol. 2013 Sep 15;178(6):962-73.

[10] FDA. Update: FDA Postlicensure Rapid Immunization Safety Monitoring (PRISM) study demonstrates no statistically significant association between Trivalent Inactivated Influenza Vaccine and Febrile Seizures in Children during the 2010-2011 influenza season. Updated May 15, 2014. http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm397611.htm; accessed 9/28/2015