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 Epidemiology (OBE) Center for Biologics Evaluation and Research (CBER)
Through:	Meghna Alimchandani, MD Deputy Director, Division of Epidemiology (DE), OBE, CBER
From:	Christopher Jason, MD Medical Officer, Pharmacovigilance Branch, DE, OBE, CBER
Subject:	Safety and Utilization Review for the Pediatric Advisory Committee
Applicant:	Seqirus, Inc.
Product:	Flucelvax Quadrivalent (influenza vaccine)
STN:	125408/330
Indication:	Flucelvax Quadrivalent is an inactivated vaccine indicated for active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. Flucelvax is approved for use in persons 4 years of age and older.
Meeting Date:	Pediatric Advisory Committee Meeting, September 2020

Contents

1 INTRODUCTION 3

1.1 Objective 3

1.2 Product Description 3

1.3 Regulatory History 4

2 MATERIALS REVIEWED 5

3 LABEL CHANGES IN REVIEW PERIOD 5

4 PRODUCT UTILIZATION DATA 5

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES 6

5.1 Pharmacovigilance Plan 6

5.2 Postmarketing Studies 8

6 ADVERSE EVENT REVIEW 9

6.1 Methods 9

6.2 Results 9

6.2.1 Deaths 10

6.2.2 Serious Non-fatal Reports 11

6.2.3 Non-serious Reports 15

6.3 Data mining 16

6.4 Periodic safety reports 17

7 LITERATURE REVIEW 17

8 CONCLUSION 18

9 RECOMMENDATIONS 18

1 INTRODUCTION

1.1 Objective

This memorandum for the Pediatric Advisory Committee (PAC) presents a comprehensive review of 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 125408/127 on May 23, 2016 to include a quadrivalent formulation, Flucelvax Quadrivalent, for use in persons 4 years of age and older.

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

Flucelvax Quadrivalent (hereby referred to as Flucelvax QIVc) is an inactivated vaccine indicated for active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. Flucelvax QIVc is approved for use in persons 4 years of age and older. For children and adolescents 4 through 17 years of age, approval is based on the immune response elicited by Flucelvax QIVc. Data demonstrating a decrease in influenza disease after vaccination of this age group with Flucelvax QIVcare not available[1].

Flucelvax QIVc is a cell-based influenza vaccine for intramuscular injection. The virus is propagated in Madin Darby Canine Kidney (MDCK) cells and contains hemagglutinin for strains of influenza A and B chosen prior to each flu season. The final product contains a total of 60 micrograms (mcg) hemagglutinin per 0.5 mL dose in the ratio of 15 mcg hemagglutinin of each of the four influenza strains. Flucelvax QIVc contains no egg protein or antibiotics. This preservative-free, non-adjuvanted vaccine is presented as a suspension for intramuscular injection supplied in 0.5 mL single-dose, prefilled syringes.

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]

[1] Flucelvax Quadrivalent U.S. package insert; updated September 19, 2019

[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 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.

1.3 Regulatory History

- May 23, 2016: FDA approval of supplement (STN 125408/127) to include a quadrivalent formulation, Flucelvax QIVc, for use in persons 4 years of age and older. **[Trigger for 2020 PAC review.]**
    - Age group ≥18 years: Flucelvax QIVc was granted "traditional approval"
    - Age group 4 years to <18 years: Flucelvax QIVc was granted approval according to the regulations for accelerated approval, 21 CFR 601.40-46.

      [*Note*: Two trials evaluating safety and immunogenicity were submitted in this supplement, one in adults ≥18 years, one in children ≥4 years to <18 years. The trials compared the quadrivalent vaccine to Flucelvax trivalent (comparator group). [3] Flucelvax trivalent received "traditional" approval in adults ≥18 years (STN 125408/0)[4] and accelerated approval in persons 4 years to <18 years (STN 125408/101)[5]]
- June 20, 2018: FDA approval of supplement (STN 125408/262) to revise the package insert to comply with the Pregnancy and Lactation Labeling Rule and to include changes to Section 6.2 *Adverse Reactions, Postmarketing Experience.*
- December 12, 2018: European Union granted marketing authorization for Flucelvax QIVc, which is marketed under the brand name *Flucelvax Tetra* outside U.S.[6]
- (b) (4) the Flucelvax QIVc accelerated approval postmarketing requirement for persons 4 years to <18 years of age.(b) (4)

[3] STN 125408/127 Flucelvax Quadrivalent Clinical Review, dated May 20, 2016, available at https://www.fda.gov/media/98178/download
[4] STN 125408/0 Flucelvax Approval Letter, dated November 20, 2012
[5] STN 125408/101 Flucelvax Approval Letter, dated May 23, 2016
[6] *Flucelvax Tetra* European Medicines Agency Product Information page https://www.ema.europa.eu/en/medicines/human/EPAR/flucelvax-tetra#authorisation-details-section

2 MATERIALS REVIEWED

- Vaccine Adverse Events Reporting System (VAERS)
    - VAERS reports for Flucelvax QIVc during May 23, 2016 to February 29, 2020 (PAC review period)
- Manufacturer's Submissions
    - Flucelvax Quadrivalent U.S. package insert; updated September 19, 2019
    - Applicant response to information request regarding dose distribution data, received April 27, 2020
    - STN (b) (4) Pharmacovigilance Plan, dated March 25, 2020
    - Periodic safety reports
    - STN 125408/325 PMC/PMR annual report
- FDA Documents
    - STN 125408/127 Flucelvax Quadrivalent Approval Letter, dated May 23, 2016
    - STN 125408/127 OBE/DE Pharmacovigilance Plan Review Memorandum
    - STN 125408/262 Flucelvax Quadrivalent Approval Letter, dated June 20, 2018
    - STN 125408/262 OBE/DE Labeling Supplement Review Memorandum
    - STN 125408/0 Flucelvax Approval Letter, dated November 20, 2012
    - STN 125408/101 Flucelvax Approval Letter, dated May 23, 2016
- Publications (see Literature Search in Section 7)

3 LABEL CHANGES IN REVIEW PERIOD

FDA approved a supplement (STN 125408/262) to revise the package insert to comply with the Pregnancy and Lactation Labeling Rule and to include updates to Section 6.2 *Postmarketing Experience*. The following preferred terms (PTs) were added to section 6.2 based on postmarketing adverse events (AEs) reported for Flucelvax QIVc: *paresthesia; generalized skin reactions including pruritus, urticaria or nonspecific rash; allergic or immediate hypersensitivity reactions, including anaphylactic shock; and syncope, presyncope*. These terms were added to the Flucelvax QIVc package insert as they were observed in the postmarket setting with Flucelvax QIVc and were previously listed in the postmarketing experience portion of the Flucelvax Trivalent (TIVc) label.

4 PRODUCT UTILIZATION DATA

Seqirus provided distribution data[7] for the US and worldwide for time intervals May 23, 2016 to February 29, 2020:

[7] These estimates were provided by the manufacturer for FDA review. Distribution data is protected as confidential commercial information and may require redaction from this review.

The total number of doses of Flucelvax QIVc distributed in the US from May 23, 2016 to February 29, 2020 was (b) (4) doses.

Seqirus estimated the number of adult and child vaccinees based on the percentage of vaccinees in each age group (b) (4) for children and (b) (4) for adults). They also based their estimate on the assumptions that the number of doses distributed was stable among influenza seasons during the time period and all distributed doses were given for vaccination. Given these assumptions, the manufacturer estimates that (b) (4) doses were administered to children aged 4-17 years and (b) (4) doses were administered to adults aged ≥18 years.
Regarding worldwide distribution, Seqirus is not able to estimate the number of doses used in pediatric and adult subpopulations. However, their total distribution worldwide (outside of the US) is (b) (4) doses during the PAC time period.
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 and some 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) is dated March 25, 2020. Important identified and potential risks, and missing information are listed in Table 1.

Table 1: Flucelvax QIVc Safety Concerns

Important Identified Risks	**Pharmacovigilance Actions**
Anaphylaxis	Routine Pharmacovigilance
Important Potential Risks	
Convulsion	Routine Pharmacovigilance
Guillain-Barré Syndrome	Routine Pharmacovigilance
Demyelination	Routine Pharmacovigilance
Vasculitis	Routine Pharmacovigilance
Immune thrombocytopenic purpura	Routine Pharmacovigilance
Missing Information	
Use in children < 2 years of age	PREA study (V130_10) to assess risk in children 6 months to 2 years of age
Use in pregnant and breastfeeding women	Pregnancy Registry Study (V130_11OB)
Safety in Immunocompromised patients	Routine Pharmacovigilance
Safety in persons with underlying diseases	Routine Pharmacovigilance

Anaphylaxis: Hypersensitivity to any component of influenza vaccine can occur post vaccination and is an Important Identified Risk. Anaphylaxis has been reported in the postmarket setting with Flucelvax QIVc. It is labeled in section 5 Warnings and Precautions and section 6.2 Postmarketing Experience in the Flucelvax QIVc USPI.

Convulsion: The exact cause of febrile seizures is not known. Febrile seizures were detected in young children in Western Australia in association with another seasonal vaccine in 2010.[8, 9] Per an Institute of Medicine report, the mechanistic cause for seizures in relation to vaccination is also unclear, though febrile seizures occur in a subset of children with fevers in the general population and thus febrile seizures may be tied to the immunogenicity of the vaccine causing fever (leading to febrile seizure) rather than a direct effect of the vaccine[10].

Demyelination: Demyelination is the pathophysiology of a variety of symptoms including acute disseminated encephalomyelitis, Guillain Barre Syndrome (described below), neuromyelitis optica, and multiple sclerosis. A review of the Vaccine Adverse Event Reporting System (VAERS) from 2006-2014 disclosed 60 cases of ADEM post influenza vaccination. The authors calculated approximately 0.5 cases of demyelination per million doses of vaccine distributed[11]. Regarding multiple sclerosis, a meta-analysis did not find evidence of an increased risk of developing multiple sclerosis or increased risk of relapse of multiple sclerosis after receiving seasonal (or H1N1) influenza[12]. As demyelination was not seen in significant numbers pre or post marketing it is not labeled in the Flucelvax QIVc USPI but it does represent a potential risk.

Vasculitis: Vasculitis has been reported after influenza vaccination, though the onset is rare with only case reports or series reported[13]. A review of safety outcomes with Optaflu in the UK found no events of vasculitis related to Optaflu vaccination in the study population that occurred in the risk window[14].

Immune Thrombocytopenic Purpura: Thrombocytopenia related to vaccination is mechanistically thought to be related to antigen mediated responses[15]. Despite this probable mechanism, thrombocytopenia has only been reported to occur post influenza vaccination in case reports[16]. A review of safety outcomes after vaccination with

---

[8] 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.

[9] 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

[10] IOM (Institute of Medicine). 2012. Adverse effects of vaccines: Evidence and causality. Washington, DC: The National Academies Press. http://www.nap.edu/catalog.php?record_id=13164

[11] Pellegrino P, Radice S, Clementi E. Acute disseminated encephalomyelitis following influenza vaccine. Epidemiology. 2015 Jan;26(1):e12-3

[12] Mailand MT, Frederiksen JL. Vaccines and multiple sclerosis: a systematic review. J Neurol. 2017 Jun;264(6):1035-1050.

[13] Watanabe, T. Vasculitis Following Influenza Vaccination: A Review of the Literature. *Curr Rheumatol Rev* **13**, 188-196 (2017).

[14] Hall GC, Davies PTG, Karim MY, Haag MDM, O'Leary C. Observational safety study of specific outcomes after trivalent cell culture seasonal influenza vaccination (Optaflu®) among adults in THIN database of electronic UK primary healthcare records. Pharmacoepidemiol Drug Saf. 2018 Jan;27(1):52-58.

[15] Perricone C, Ceccarelli F, Nesher G, Borella E, Odeh Q, Conti F, Shoenfeld Y, Valesini G. Immune thrombocytopenic purpura (ITP) associated with vaccinations: a review of reported cases. Immunol Res. 2014 Dec;60(2-3):226-35.

[16] Hamiel U, Kventsel I, Youngster I. Recurrent Immune Thrombocytopenia After Influenza Vaccination: A Case Report. Pediatrics. 2016 Dec;138(6).

Optaflu in the UK disclosed cases of thrombocytopenia post vaccination but not at an increased rate versus the background[17].

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,[18] and is routinely listed in the label of influenza vaccines.

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 Flucelvax QIVc. The sponsor is also conducting a pregnancy registry as a postmarketing commitment (PMC) study (please see section 5.2).

5.2 Postmarketing Studies

Current status[19] of postmarketing studies listed in May 23, 2016 approval letter for STN 125408/127 are summarized in Table 2.

Table 2: Flucelvax QIVc postmarketing studies

Accelerated Approval required study #1: To conduct a study to evaluate the efficacy, safety and immunogenicity of the quadrivalent formulation of your Influenza Vaccine compared to a non-influenza comparator vaccine in persons 4 years to <18 years of age. *Revised study name:* V130_12; A Phase III/IV, Stratified, Randomized, Observer Blind, Multicenter Clinical Study to Evaluate the Efficacy, Safety and Immunogenicity of a Cell-Based Quadrivalent Subunit Influenza Virus Vaccine Compared to Non-Influenza Comparator Vaccine in Subjects ≥ 2 years to <18 Years of Age.	
Current Status	Delayed
Enrollment	Enrollment closed with total 4514 subjects enrolled
Study Milestones	*Original study milestones listed in STN 125408/127 approval letter:* Final Protocol Submission: September 30, 2016 Study Completion: March 30, 2017 Final Report Submission: August 30, 2018 *The study was delayed and actual dates are as follows:* Study completion: September 30, 2019 Final report submission: (b) (4)

[17] Hall GC, Davies PTG, Karim MY, Haag MDM, O'Leary C. Observational safety study of specific outcomes after trivalent cell culture seasonal influenza vaccination (Optaflu®) among adults in THIN database of electronic UK primary healthcare records. Pharmacoepidemiol Drug Saf. 2018 Jan;27(1):52-58.
[18] 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.
[19] STN 125408/325 PMC/PMR annual report dated January 16, 2020, covering November 21, 2018 to November 20, 2019

Pediatric required study under Pediatric Research Equity Act (PREA): Deferred pediatric study (Study V130_10) to evaluate the safety and immunogenicity of your quadrivalent formulation of Influenza Vaccine in subjects 6 months to < 4 years of age.	
Current Status	Ongoing
Enrollment	Enrollment closed with total 2414 subjects enrolled
Study Milestones	Final Protocol submission: June 30, 2019 Study completion: August 30, 2020 Final report submission: February 28, 2021
Postmarketing commitment study #3: To establish a pregnancy registry to prospectively collect data on spontaneously-reported exposures to Flucelvax Quadrivalent or Flucelvax during pregnancy and collect data on pregnancy outcomes. When the registry has enrolled a minimum of 600 evaluable subjects and collected data on the outcomes specified in the protocol, Seqirus will submit a full study report and continue enrolling in the registry pending CBER review and discussion of registry results with Seqirus.	
Current Status	Ongoing
Enrollment	As of September 4, 2019, 514 pregnant women have been enrolled in the study.
Study Milestones	Final Protocol submission: December 16, 2015 Study completion: August 31, 2020 Final Report Submission: January 31, 2021

6 ADVERSE EVENT REVIEW

6.1 Methods

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event reports following use of Flucelvax QIVc between May 23, 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 Flucelvax QIVc during the PAC review period are listed in Table 3 below. There were 4,478 US and 4 foreign reports for review period May 23, 2016 to February 29, 2020.

Table 3: VAERS Reports for Flucelvax QIVc during May 23, 2016 – February 29, 2020

Age (years)	Serious Non-Fatal*		Deaths		Non-Serious		Total Reported	
	US	Foreign	US	Foreign	US	Foreign	US	Foreign
<4	34	0	1	0	96	0	131	0
4 to < 18	47	0	0	0	424	0	471	0
≥ 18	287	2	5	0	3288	1	3580	3
Unknown	96	1	0	0	200	0	296	1
All Ages	464	3	6	0	4008	1	4478	4

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

6.2.1 Deaths

There were 6 deaths following Flucelvax QIVc during the PAC review period, including one pediatric death. The fatal reports were individually reviewed and are summarized below.

6.2.1.1 Infant Death

A neonate died 24 hours after birth with congenital polycystic kidney disease causing anhydramnios and other unreported complications after mother was vaccinated with Flucelvax QIVc at 16 weeks. Mother was 30-years-old with medical history of yeast infection, Herpes simplex virus (HSV), migraines, anxiety, and neurofibromatosis. Concomitant medications included terconazole and Zoloft. The mother's obstetrical history was 5 prior pregnancies; 2 full term live births, 2 preterm live births, and 1 elective abortion. There was no prior maternal or paternal history of major congenital malformation (MCM) and no prior illicit drug use, but there was a history of alcohol use (2 or less). She was vaccinated with Flucelvax QIVc at week 16 (b) (6) and ultrasound (US) and Quad screen 2 days later (b) (6) showed no MCMs. Starting at week 28 consecutive US showed polycystic kidneys and anhydramnios. Mother gave birth to a 2.7 kg female at 36.3 weeks with APGAR at 1,5,10 minutes 1,3,5 respectively. Infant died within 24 hours and cause of death was reported as unknown.

Reviewer comment: Information regarding autopsy was not reported. The role of Flucelvax QIVc fetal exposure during pregnancy and causality assessment is precluded by limited information and confounded by factors such as mother's medical history of HSV 2, neurofibromatosis, and multiple concomitant medications. The sponsor and reporter's assessment of fetal exposure during pregnancy was assessed as not related. Of note, the mother was enrolled in the pregnancy registry PMC study (see section 5.2), and this case was also reported to the pregnancy registry.

6.2.1.2 Adult Deaths

- A 92-year-old female died of acute disseminated encephalomyelitis (ADEM) (b) (6) months after receiving Flucelvax QIVc. Patient was admitted to hospital with

Non-ST segment elevation myocardial infarction (NSTEMI) and ADEM and died later that day as comfort measures were initiated. Onset of ADEM was 91 days post vaccination.

- A 41-year-old male died of cardiac arrest during a seizure (b) (6) days after vaccination with Flucelvax QIVc. Patient's medical history consisted of Marfan Syndrome and aortic aneurysm preparing for surgery. Patient was not able to be resuscitated and died in the ER.

- A 71-year-old male died at home (b) (6) days after receiving Flucelvax QIVc. Patient had a history of hypertension, hyperlipidemia, and diabetes mellitus. Per death certificate his cause of death was ischemic heart disease.

- A 63-year-old male died within (b) (6) of vaccination with Flucelvax QIVc. Patient was shivering prior to receiving vaccine and "felt cold". Patient was vaccinated and provider asked family to pick him up. Son arrived 50 minutes post vaccination and 5 minutes later patient got weak with shallow breathing and EMS arrived. Patient lost pulse, was given CPR, and transported to Emergency Department where he died of cardiac arrest. The underlying cause of death was not reported.

- A 75-year-old female died of Guillain Barre Syndrome (GBS) (b) (6) months after receiving influenza vaccine. Onset of symptoms was 3 days post vaccination. She was hospitalized (b) (6) post vaccination and died (b) (6) months post vaccination.

Reviewer comment: Most death reports contained minimal case details and several patients had other diagnoses that may have contributed to the fatal outcomes. The role of Flucelvax QIVc and causality assessment was limited by paucity of information provided in these death reports.

6.2.2 Serious Non-fatal Reports

During the PAC review period, there were 467 serious non-fatal reports; 81 of which involved pediatric patients. All pediatric serious non-fatal reports were U.S. reports. Adult serious non-fatal reports included 287 U.S. reports and 2 foreign reports. Age was unknown for the remaining 97 serious non-fatal reports.

The most common Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) are displayed for pediatric patients and adult patients (see Tables 4 and 5). Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

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

Preferred Term (PT)	Number of Serious Reports	Label* Status
Foetal Exposure During Pregnancy	35	*Unlabeled*
Influenza	28	WP
Vaccination Failure	28	WP
Premature baby	23	*Unlabeled*
Caesarean section	18	*Unlabeled*
Low birth weight baby	15	*Unlabeled*
Cough	7	Unlabeled
Urticaria	6	PM
Headache	5	CT
Pyrexia	5	CT
Chills	3	CT
Fatigue	3	CT
Nausea	3	CT
Rash	3	PM
Twin Pregnancy	3	*Unlabeled*

*Label dated September 19, 2019
Label Sections: Section 5 Warnings and Precautions (WP), Section 6 Adverse reactions 6.1 Clinical Trials (CT) or Post Marketing (PM) Experience
Note: Above table displays PTs occurring with a frequency of ≥3 reports.

Most of the MedDRA (preferred terms) PTs are labeled events or consistent with an already labeled event. Please see below for additional discussion on PTs.

PTs related to reports from ongoing pregnancy registry study: *Foetal Exposure During Pregnancy; Premature baby; Caesarean section; Low birth weight baby; Twin Pregnancy*

The study V130_11OB is an ongoing pregnancy registry study involving Flucelvax TIVc and QIVc. As part of the study protocol, pregnant women who are not enrolled prior to Flucelvax vaccination and experience AEs are not analyzed with the prospectively followed registry population. Instead, the sponsor is reporting these retrospective cases as they are made aware of them to the VAERS database. Exposure during pregnancy is not an adverse event. All pregnancies have a risk of birth defect, loss, or other adverse outcomes. Note that premature delivery or preterm birth, defined as those occurring less than 37 weeks gestation occurs in 9.93% to 10.02% of births in 2017 according to a National Center for Health Statistics report[20]. Similarly, the rate of low birthweight babies, defined as less than 2.5 kg, was 8.28% in 2018[21]. Given the rates of

[20] https://www.cdc.gov/nchs/data/databriefs/db346-h.pdf
[21] https://www.cdc.gov/nchs/data/nvsr/nvsr68/nvsr68_13-508.pdf

these events in the general population, there are no new safety concerns identified from cases reported to VAERS.

PTs related to cases of influenza A infections reported by a school nurse: *Influenza; Vaccination failure; Cough*

Of the 28 reports involving the PT "vaccination failure," 25 reports contained information on laboratory diagnosis/confirmation of influenza A/B and 3 reports had no mention of laboratory confirmation of influenza. In addition, 23 of the 28 reports involving vaccination failure were reported by a single reporter. The reporter, a school nurse, submitted VAERS reports involving 23 students aged 14-18 years at one academic institution who were vaccinated during the 2016-2017 influenza season. All reports involved vaccination failure. Note that the reports retrieved in VAERS represent a small number of reports compared to the (b) (4) doses estimated to have been distributed during the review period. Additionally, vaccination failure is not disproportionally reported for Flucelvax QIVc compared to other vaccines in the VAERS database. [see section 6.3 Data Mining]. Additionally, such reports are often indeterminate due to missing information on influenza virus diagnostic test results. Influenza vaccines are not 100% effective: influenza in some vaccinated patients can be expected, particularly in years in which the strains included in the vaccine do not correlate well with the strains circulating in the population. It was reported that the 2016 – 2017 influenza vaccines provided moderate protection against any influenza among outpatients but were less protective against influenza A (H3N2) viruses than B viruses[22]. Flucelvax QIVc label includes Warnings and Precautions, section 5.5, Limitations of Vaccine Effectiveness, "*Vaccination with FLUCELVAX QUADRIVALENT may not protect all vaccine recipients against influenza disease*." The PTs *Influenza, vaccination failure*, *cough, fever* and other related symptoms are related to the reports involving the patients that received Flucelvax QIVc and developed influenza disease.

Table 5: Most frequently reported PTs for adult (≥ 18 years) serious non-fatal reports

Preferred Term (PT)	Number of Serious Reports	Label* Status
Exposure during pregnancy	122	*Unlabeled*
Caesarean section	44	*Unlabeled*
Paraesthesia	42	WP, PM
Pain	41	CT
Delivery	39	*Unlabeled*
Hypoaesthesia	36	*Unlabeled*
Asthenia	35	*Unlabeled*
Muscular Weakness	35	*Unlabeled*
Guillain-Barre Syndrome	34	WP
Premature delivery	32	*Unlabeled*

[22] Flannery et al. Influenza Vaccine Effectiveness in the United States During the 2016-2017 Season. Clin Infect Dis. 2019 May 17; 68 (11): 1798-1806.

Preferred Term (PT)	Number of Serious Reports	Label* Status
Pyrexia	27	CT
Anaemia	26	*Unlabeled*
Dizziness	26	*Unlabeled*
Dyspnoea	26	*Unlabeled*
Pain in Extremity	26	CT
Gait disturbance	25	*Unlabeled*
Headache	24	CT
Fall	19	WP, PM
Immunoglobulin therapy	19	*Unlabeled*
Influenza	19	WP
Cough	18	*Unlabeled*
Musculoskeletal pain	18	CT
Nausea	16	CT
Malaise	15	*Unlabeled*
Myalgia	15	CT
Vomiting	15	CT
Back Pain	14	*Unlabeled*
Condition Aggravated	14	Not an AE
Constipation	14	*Unlabeled*

*Label dated September 19, 2019
Label Sections: Section 5 Warnings and Precautions (WP), Section 6 Adverse reactions 6.1 Clinical Trials (CT) or Post Marketing (PM) Experience
Note: Above table displays PTs occurring with a frequency of ≥14 reports.

Most reported PTs are labeled events or consistent with an already labeled event or are non-specific signs or symptoms. PTs related to reports from the ongoing pregnancy registry study were previously discussed. In this table, the AEs reported are associated with the mother as the sponsor submits 2 reports for each pregnant patient, one for the mother and one for the neonate. There is no new information in these reports, and the PTs "*exposure during pregnancy, caesarean delivery, delivery*" are not AEs but describe events during pregnancy. Similarly, PTs "*Influenza, malaise, cough*" are related to occurrence of influenza-like illness and limitations of vaccine effectiveness (WP) as described above.

The serious AEs in the adult age group also reflect the different complications for which patients in this population are at higher risk. The PT's "*hypoaesthesia, asthenia, muscular weakness, gait disturbance*, and *immunoglobulin therapy"* are related to the known AEs Guillain-Barre Syndrome (GBS), paresthesia and swelling of injected limb which is listed in the postmarketing experience section of the USPI. The PT "*dizziness*" was related to GBS and syncope (also listed in the postmarketing section of USPI). The PTs "*Anemia, Constipation*" were in reports that were either describing GBS or pregnancy. This is reasonable as both anemia and constipation can occur in patients hospitalized with GBS. In addition, constipation and anemia are known to occur in

pregnancies; constipation in up to 50%[23], and anemia in 5.4% of pregnancies[24]. The PT "*Dyspnoea*" was related to influenza infection and GBS in the reports sent to the VAERS system involving Flucelvax.

6.2.3 Non-serious Reports

During the reporting period, there were 4,009 non-serious reports; 520 of which involved pediatric patients. Table 6 below lists the most frequently reported PTs in pediatric non-serious reports. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 6: Most frequently reported PTs for pediatric (<18 years) non-serious reports

Preferred Term (PT)	Number of Serious Reports	Label* Status
No adverse event	122	Not an AE
Product administered to patient of inappropriate age	67	Not an AE
Injection site erythema	66	CT
Loss of consciousness	61	WP, PM
Syncope	60	WP, PM
Injection site swelling	58	CT
Erythema	45	CT
Dizziness	44	WP, PM
Product Storage Error	44	Not an AE
Injection site warmth	39	CT
Pallor	36	*Unlabeled*
Warmth	30	CT
Skin Warm	28	CT
Rash	22	PM
Drug Administered to patient of inappropriate age	21	Not an AE
Nausea	21	CT
Swelling	20	PM
Injection site pain	19	CT
Urticaria	19	PM
Vomiting	19	CT
Peripheral Swelling	16	PM
Hyperhidrosis	15	*Unlabeled*
Injection site pruritis	15	CT

[23]Zielinski R et al Gastrointestinal distress in pregnancy: prevalence, assessment, and treatment of 5 common minor discomforts. J Perinat Neonatal Nurs. 2015 Jan-Mar;29(1):23-31. doi: 10.1097/JPN.0000000000000078.
[24]Sun et al, Anemia in Pregnancy: A Pragmatic Approach. Obstet Gynecol Surv. 2017 Dec;72(12):730-737. doi: 10.1097/OGX.0000000000000510

Preferred Term (PT)	Number of Serious Reports	Label* Status
Head Injury	13	*Unlabeled*
Fatigue	12	CT
Malaise	12	*Unlabeled*
Pyrexia	12	CT
Pruritis	11	PM
Abdominal pain upper	10	*Unlabeled*
Cold Sweat	10	*Unlabeled*

*Label dated September 19, 2019
Label Sections: Section 5 Warnings and Precautions (WP), Section 6 Adverse reactions 6.1 Clinical Trials (CT) or Post Marketing (PM) Experience
Note: PTs occurring with a frequency ≥ 10 reports is displayed in above table

Most reported PTs are labeled events or consistent with an already labeled event or non-specific PTs. The PTs "*Product administered to patient of inappropriate age,"* and *"drug administered to patient of inappropriate age*" involve 95 unique reports of patients vaccinated who are between the ages of 6 months and 3 years of age (Flucelvax QIVc is approved in persons ≥4 years of age). In the reports sent to VAERS there were no AEs associated with these reports, described by the PT, "*no adverse event*."

The reports involving the PT for "*product storage error*" also did not involve AEs and were coded with the PT "*no adverse event*". The PTs "*head injury, hyperhidrosis*" were related to syncope events. Syncope is a known adverse event and is labeled in Warnings and Precautions as well as Postmarketing Experience sections in the Flucelvax QIVc USPI. The reports involving the PT "*abdominal pain*" were related to a systemic response to the vaccine and were accompanied by myalgia and vomiting in the reports in VAERS. In the reports, the patients all recovered.

The most common PTs for adult non-serious reports included: *Injection Site Pain* (497 reports), *Pain in Extremity* (457 reports), *Pain* (404 reports), *No Adverse Event* (353 reports), *Injection Site Erythema* (316 reports), and *Injection Site Swelling* (261 reports). These reports involve PTs that are known local reactions to vaccination. These adverse events are labeled in Section 6 Adverse Reactions in the Flucelvax QIVc USPI.

6.3 Data mining

Data mining was performed to evaluate whether any reported events following the use of Flucelvax QIVc 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, identified 8 PTs with a disproportional reporting alert for Flucelvax QIVc listed in Table 7 (EB05>2; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean). Of note, these PTs are not mutually

exclusive; a single report can include multiple PTs.

Table 7: Data mining results

Preferred Term (PT) with EB05>2	Number of Reports	Label* Status
Caesarean Section	41	*Unlabeled*
Foetal Exposure during pregnancy	72	*Unlabeled*
Apgar score normal	49	*Unlabeled*
Premature baby	40	*Unlabeled*
Low birth weight baby	21	*Unlabeled*
Apgar score low	7	*Unlabeled*
Exposure during pregnancy	16	*Unlabeled*
Twin Pregnancy	5	*Unlabeled*

*Label dated September 19, 2019
Label Sections: Section 5 Warnings and Precautions (WP), Section 6 Adverse reactions 6.1 Clinical Trials (CT) or Post Marketing (PM) Experience

These PTs were related to reports from the ongoing pregnancy study, and appeared among the most frequently reported PTs previously discussed in Section 6.2 of this memo. *Caesarean section* is not an adverse event and describes an obstetric therapeutic procedure. *Twin pregnancy* is not an adverse event. *Fetal exposure during pregnancy and Exposure during pregnancy* are not adverse events and describe the pregnant women who received Flucelvax QIVc and enrolled in the ongoing pregnancy registry. *Low birth weight baby, Apgar score normal, Apgar score low, Premature baby*, describe pregnancy outcomes. All pregnancies have a risk of birth defect, loss, or other adverse outcomes (please see section 6.2 for additional discussion). Furthermore, the increased disproportional reporting could reflect the widespread use of Influenza vaccines (including Flucelvax QIVc) during pregnancy (per ACIP recommendations) compared to other vaccines included in the comparison group in disproportionality analysis. There are no new safety concerns identified from data mining results.

6.4 Periodic safety reports

The manufacturer's postmarketing periodic safety reports for Flucelvax QIVc 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 8, 2020, for peer-reviewed literature, with the search term "Flucelvax Quadrivalent" and "safety" limited by human species, and dates from PAC trigger (May 23, 2016) to date of search (February 29, 2020), retrieved 2 publications pertaining to safety. No new safety concerns for Flucelvax QIVc were identified in the review of these publications, summarized in the table below:

Publication	Authors' Safety Conclusion
Cell-Based Quadrivalent Inactivated Influenza Virus Vaccine (Flucelvax® Tetra/Flucelvax Quadrivalent®): A Review in the Prevention of Influenza. Lamb YN. Drugs. 2019 Aug;79(12):1337-1348. doi: 10.1007/s40265-019-01176-z.	Flucelvax trivalent (TIVc) and quadrivalent (QIVc) formulations are cell-based vaccines produced using a mammalian cell line rather than embryonated chicken eggs. Pivotal phase III clinical trials in adult and pediatric subjects demonstrated the immunogenicity of QIVc to be noninferior to that of TIVc. QIVc was generally well tolerated in clinical trials. In adult and pediatric QIVc recipients, the most common solicited adverse reactions were injection site pain and headache. Reactogenicity was comparable to that of TIVc; no safety signals unique to QIVc emerged.
Flucelvax Tetra: a surface antigen, inactivated, influenza vaccine prepared in cell cultures. Bühler S, Ramharter M. ESMO Open. 2019 Jan 21;4(1):e000481. doi: 10.1136/esmoopen-2018-000481.	Side effects involving Flucelvax were of "expected nature."

8 CONCLUSION

This postmarketing pediatric safety review was triggered by the May 23, 2016 approval to include a quadrivalent formulation, Flucelvax QIVc, for use in persons 4 years of age and older. Review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for Flucelvax QIVc does not indicate any new safety concerns. There was a single pediatric death. 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 Flucelvax QIVc.