



**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)

From: Meghna Alimchandani, MD
Deputy Director, Division of Epidemiology (DE), OBE, CBER

Subject: Safety and Utilization Review for the Pediatric Advisory Committee

Applicant: Seqirus, Inc.

Product: Flucelvax (influenza vaccine)

STN: 125408/330

Indication: Flucelvax 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.....	3
2	MATERIALS REVIEWED	4
3	LABEL CHANGES IN REVIEW PERIOD.....	4
4	PRODUCT UTILIZATION DATA	5
5	PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES.....	5
5.1	Pharmacovigilance Plan.....	5
5.2	Postmarketing Studies.....	6
6	ADVERSE EVENT REVIEW	7
6.1	Methods	7
6.2	Results	8
6.2.1	Deaths.....	8
6.2.2	Serious Non-fatal Reports.....	8
6.2.3	Non-serious Reports.....	9
6.3	Data mining	10
6.4	Periodic safety reports.....	10
7	LITERATURE REVIEW.....	10
8	CONCLUSION.....	11
9	RECOMMENDATIONS.....	11

1 INTRODUCTION

1.1 Objective

This memorandum for the Pediatric Advisory Committee (PAC) presents a comprehensive review of the postmarketing pediatric safety covering a period including 18 months following the approval in accordance with Section 505B (i) (1) of the Food and Drug Cosmetic Act [21 U.S.C. §355c]. The trigger for this pediatric postmarketing safety review was the approval of BLA supplement 125408/101 for Flucelvax on May 23, 2016 to extend the age range for use of Flucelvax to include persons 4 years to <18 years of age according to the regulations for accelerated approval.

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 is a trivalent inactivated influenza vaccine that contains the purified surface proteins (hemagglutinin and neuraminidase) from influenza virus subtypes A and type B. The final product contains a total of 45 micrograms (mcg) hemagglutinin per 0.5 mL dose in the ratio of 15 mcg hemagglutinin each of the three influenza strains. The antigens contained in Flucelvax are derived from virus propagated in Madin Darby Canine Kidney (MDCK) cells. 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.¹

1.3 Regulatory History

- June 1, 2007: European Union (EU) granted marketing authorization for Optaflu for use in adults ≥18 years. Flucelvax is marketed under the brand name "Optaflu" outside US.

Note: The EU marketing authorization for Optaflu expired in 2017 *following the decision of the marketing authorisation holder, Seqirus GmbH, not to apply for a renewal of the marketing*

¹ 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>

authorisation.²

- November 20, 2012: FDA initial approval of Flucelvax (STN 125408/0) for active immunization against influenza for use in adults ≥ 18 years.
- May 23, 2016: FDA approval of supplement (STN 125408/101) to extend the age range to include persons 4 years to <18 years according to the regulations for accelerated approval. **[Trigger for this PAC review.]**
- May 23, 2016: FDA approval of Flucelvax Quadrivalent supplement (STN 125408/127) for use in persons ≥ 4 years.
FDA evaluated two trials evaluating safety and immunogenicity, one in adults ≥ 18 years, one in children ≥ 4 years to <18 years. The trials compared the quadrivalent vaccine to Flucelvax TIV (comparator group).

2 MATERIALS REVIEWED

- Vaccine Adverse Events Reporting System (VAERS)
 - VAERS reports for Flucelvax during May 23, 2016 to February 29, 2020
- Manufacturer's Submissions
 - Flucelvax US package insert, dated April 2016
 - Applicant response to information request regarding dose distribution data, received April 27, 2020
 - Optaflu Pharmacovigilance Plan, version 2.0, dated May 2011
 - Periodic safety reports
- FDA Documents
 - Flucelvax Approval Letter for BLA 125408/0, dated November 20, 2012
 - Flucelvax Approval Letter for BLA 125408/101, dated May 23, 2016
 - Flucelvax Quadrivalent Approval Letter for BLA 125408/101, dated May 23, 2016
 - OBE/DE Pharmacovigilance Plan Review Memorandum for BLA 125408/101
 - OBE/DE Pharmacovigilance Plan Review Memorandum for 125408/0
- Publications (see Literature Search in Section 7)

3 LABEL CHANGES IN REVIEW PERIOD

There have been no label changes related to safety concerns for Flucelvax during May 23, 2016 to February 29, 2020 (PAC review period).

² European Medicines Agency Public Statement Optaflu, dated June 22, 2017. Available: https://www.ema.europa.eu/en/documents/public-statement/public-statement-optaflu-expiry-marketing-authorisation-european-union_en.pdf

4 PRODUCT UTILIZATION DATA

Seqirus provided Flucelvax distribution data³ for the PAC review period May 23, 2016 to February 29, 2020:

- There were (b) (4) doses of Flucelvax distributed in the US or outside US
[Note that from (b) (4)]

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan

The manufacturer's current Pharmacovigilance Plan (PVP), version 2.0, is dated May 2011. The sponsor conducts routine pharmacovigilance for the safety concerns described in Table 1.

Table 1: Flucelvax Safety Concerns

Important Identified Risks
None
Important Potential Risks
Neuritis
Convulsion
Anaphylaxis
Encephalitis
Vasculitis
Guillain-Barré Syndrome
Demyelination
Bell's palsy
Immune thrombocytopenia
Missing Information
Use in infants and toddlers
Safety in subjects with underlying diseases or immunocompromised patients
Use in pregnant women

There was no important identified risk for Flucelvax.

The sponsor included 9 important potential risks, for events reported following other seasonal influenza vaccines and considered adverse events of special interest (AESI): neuritis, convulsion, anaphylaxis, encephalitis, vasculitis, Guillain-Barré Syndrome (GBS), demyelination disorders, Bell's palsy, and immune thrombocytopenia. No cases of neuritis, encephalitis, vasculitis, GBS, demyelination, Bell's palsy, or immune thrombocytopenia were observed during the pre-licensure studies for Flucelvax.

³ 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.

Convulsion: The cause of febrile seizures is not known. Febrile seizures have been reported following Flucelvax in pre-licensure studies. Febrile seizures have been reported for other influenza vaccines.

Anaphylaxis: Hypersensitivity to any component of influenza vaccine can occur post vaccination. History of severe allergic reactions including anaphylaxis to any component of the vaccine is a Contraindication. Preventing and Managing Allergic Reactions is also labeled under section 5 *Warnings and Precautions*. Anaphylactic reaction is also included under section 6.2 *Postmarketing Experience*.

Guillain-Barré Syndrome (GBS): Guillain-Barré Syndrome (GBS) is labeled under section 5 *Warnings and Precautions*. GBS was associated with use of an A/New Jersey 1976 influenza vaccine in anticipation of a swine influenza epidemic, and is routinely listed in the label of influenza vaccines.⁴

The safety concerns 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 safety-related postmarketing requirement (PMR) studies under Food and Drug Administration Amendments Act (FDAAA) or Risk Evaluation and Mitigation Strategy (REMS) for Flucelvax. The sponsor is also conducting a pregnancy registry as a postmarketing commitment (PMC) study (please see section 5.2).

5.2 Postmarketing Studies

Pregnancy registry postmarketing commitment (PMC)

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. The registry will enroll a minimum of 600 evaluable subjects and collect data on the various pregnancy outcomes specified in the protocol.⁵

Study completion: August 31, 2020

Final Report Submission: January 31, 2021

Status: Ongoing

Enrollment: As of September 4, 2019, 514 pregnant women have been enrolled.⁶

Pediatric postmarketing requirements (PMR) under the Pediatric Research Equity Act

4 years to < 18 years:

The applicant has completed Study V58_31 which evaluated the safety and immunogenicity of Flucelvax in children 4 years to < 18 years.⁷

[Note: This was the basis for approval of STN 125408/101 to extend the age range for use of Flucelvax to

⁴ 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.

⁵ Approval letter for STN 125408/127, dated May 23, 2016

⁶ STN 125408/325 PMC/PMR annual report, covering November 21, 2018 to November 20, 2019

⁷ STN 125408/101 approval letter dated May 23, 2016 and STN 125408/0 approval letter dated November 20, 2012

include persons 4 years to <18 years; the trigger for this PAC review.]

6 months to < 4 years:

The applicant was released from a PREA PMR (Study V58_35) to evaluate the safety and immunogenicity of Flucelvax in children ages 6 months to < 4 years, which was replaced by a new PREA PMR study, Study V130_10, in infants and children 6 months to < 4 years of age, using Flucelvax quadrivalent formulation.⁸

Final Protocol submission: June 30, 2019

Study completion: August 30, 2020

Final report submission: February 28, 2021

Status: Ongoing

Accelerated approval PMR⁹

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.

Final Protocol Submission: September 30, 2016

Study Completion: March 30, 2017

Final Report Submission: August 30, 2018

Revised study milestones:

Study Completion: September 30, 2019

Final Report Submission: March 31, 2020

Status: Delayed

[Note: Final study report (b) (4)]

6 ADVERSE EVENT REVIEW

6.1 Methods

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event reports following use of Flucelvax 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.

⁸ STN 125408/101 approval letter dated May 23, 2016

⁹ STN 125408/101 approval letter dated May 23, 2016

6.2 Results

The results of the VAERS search of AE reports for Flucelvax during the PAC review period are listed in Table 2 below. There were 44 US and 50 foreign reports for the review period May 23, 2016 to February 29, 2020.

Table 2: VAERS Reports for Flucelvax during May 23, 2016 to February 29, 2020

Age	Serious non-fatal, US	Serious Non-fatal, Foreign	Deaths, US	Deaths, Foreign	Non-Serious, US	Non-Serious, Foreign	Total, US	Total, Foreign
<18 years	0	4	0	0	20	0	20	4
≥18 years	3	38	0	0	15	0	18	38
Unknown	2	8	0	0	4	0	6	8
All ages	5	50	0	0	39	0	44	50

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

6.2.1 Deaths

There were no deaths following Flucelvax during the PAC review period.

6.2.2 Serious Non-fatal Reports

During the PAC review period, there were 55 serious non-fatal reports, of which 4 were pediatric.

Upon further review of the narratives of the pediatric reports, one case did not involve an adverse event and was submitted as otherwise medically important conditions (OMIC). Narratives for the remaining 3 pediatric foreign reports are provided below.

- 16-year-old female with past medical history of asthma was administered Optaflu, and approximately 3 months later, developed Henoch-Schonlein purpura. Clinical details were not provided.
- 16-year-old male experienced onset of abdominal pain 14 hours after vaccination with Optaflu. The abdominal pain worsened, and he developed fever, leukocytosis (WBC 17,000), and was hospitalized. Appendicitis was excluded by ultrasound. Outcome of the events was reported as condition improving.
- 17-year-old female with past medical history that included episodes of syncope after blood tests, was administered Optaflu and within five minutes “fainted in a chair.” As per the report, “The patient was laid on floor. The patient was breathing but started drooling and was unresponsive for a few minutes.” The patient was subsequently monitored by paramedics and the reaction was confirmed to be syncope and not an anaphylactoid reaction. Outcome of the events was reported as condition improving.

Reviewer comment: Causality assessment is precluded by limited information in foreign reports. Syncope is a labeled event (*Warnings and Precautions; Postmarketing Experience*) for Flucelvax. There are no new safety concerns from review of these reports.

The most frequently reported Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) for serious non-fatal reports in adults 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 in adult (>18 years) serious reports

Preferred Term (PT)	Number of Serious Reports	Label* Status
Malaise	7	Labeled (<i>6.1 Clinical Trials Experience</i>)
Dizziness	6	Unlabeled
Paraesthesia	6	Labeled (<i>6.2 Postmarketing Experience</i>)
Syncope	6	Labeled (<i>5.4 Warnings and Precautions; 6.2 Postmarketing Experience</i>)
Hypoaesthesia	5	Unlabeled
Myalgia	5	Labeled (<i>6.1 Clinical Trials Experience</i>)
Pyrexia	5	Labeled (<i>Fever is labeled under 6.1 Clinical Trials Experience</i>)
Arthralgia	4	Labeled (<i>6.1 Clinical Trials Experience</i>)
Diarrhoea	4	Unlabeled
Hyperhidrosis	4	Unlabeled
Loss of consciousness	4	Unlabeled

*Flucelvax label, dated April 2016

Note: PTs occurring with a frequency >3 reports are shown in Table 3.

Most reported PTs are labeled events or consistent with an already labeled event or non-specific events. *Dizziness* and *Loss of consciousness* are related to labeled events *Presyncope* (6.2 Postmarketing Experience) and *Syncope* (5.4 Warnings and Precautions; 6.2 Postmarketing Experience). *Hypoaesthesia* may occur with other neurologic symptoms. *Diarrhea* may be related to an infectious process or other underlying conditions. *Hyperhidrosis* is a non-specific event. No new safety concerns were identified from review of most frequently reported PTs.

6.2.3 Non-serious Reports

During the reporting period, there were 39 US non-serious reports; 20 of which involved pediatric patients.

PTs for non-serious pediatric reports included events not related to occurrence of an adverse event: *No adverse event* (N = 15); *Wrong drug administered* (N = 6); *Unevaluable event* (N = 4); and *Drug administered to patient of inappropriate age* (N = 3). These PTs are not mutually exclusive; a single report can include multiple PTs. Additionally, PTs for *Decreased appetite* (N = 1) and *Pyrexia* (N = 1) were reported for non-serious pediatric AEs. *Decreased appetite* is a non-specific event that is unlabeled. *Fever* is a labeled event (Section 6.1 Clinical Trials Experience).

PTs for non-serious adult reports also included events not associated with occurrence of an adverse event: *No adverse event* (N = 10); *Incorrect product storage* (N = 7); and *Expired product administered* (N = 2). There were 2 reports for *Urticaria*, which is a labeled event (6.2 Postmarketing Experience). All remaining PTs were reported with single sporadic non-serious AEs.

No new safety concerns were identified from review of most frequently reported PTs.

6.3 Data mining

Data mining was performed to evaluate whether any reported events following the use of Flucelvax were disproportionately 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 23, 2020, identified 2 PTs with a disproportional reporting alert for Flucelvax (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. The 2 PTs were:

- Product administered to patient of inappropriate age (N = 81)
- Product use issue (N = 28)

Most reports for *Product administered to patient of inappropriate age* and *Product use issue*, involved pediatric patients who received the vaccine prior to 2016, when Flucelvax was approved in adults ≥ 18 years of age. (In 2016, Flucelvax was approved in persons ≥ 4 years of age, which is the trigger for this PAC review.) These reports were not associated with adverse events.

6.4 Periodic safety reports

The manufacturer's postmarketing periodic safety reports for Flucelvax were reviewed. The adverse events 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 30, 2020, for peer-reviewed literature, with the search term "Flucelvax" and "safety" limited by human species, and publication dates from PAC trigger (May 23, 2016) to date of search (April 30, 2020), retrieved 1 publication pertaining to safety. No new safety

concerns for Flucelvax were identified in the review of this publication, summarized below:

	Authors' Safety Conclusion
<p>Lamb YN. Cell-Based Quadrivalent Inactivated Influenza Virus Vaccine (Flucelvax® Tetra/Flucelvax Quadrivalent®): A Review in the Prevention of Influenza. <i>Drugs</i>. 2019 Aug;79(12):1337-1348. Review. Erratum in: <i>Drugs</i>. 2019 Dec;79(18):2009.</p>	<p>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.</p>

8 CONCLUSION

This postmarketing pediatric safety review was triggered by the May 23, 2016 approval to extend the age range for use of Flucelvax to include persons 4 years to <18 years of age. Review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for Flucelvax does not indicate any new safety concerns. No deaths were reported during this review period. There were very few serious pediatric reports. Adverse events in serious reports were generally consistent with the safety data in pre-licensure studies and listed in the label. No unusual frequency, clusters, or other trends for adverse events were identified that would suggest a new safety concern.

9 RECOMMENDATIONS

FDA recommends continued routine safety monitoring of Flucelvax.