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: Seqirus Pty Ltd. (Seqirus)

Product: Afluria Quadrivalent (influenza vaccine)

STN: 125254/828

Indication: Afluria quadrivalent is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine; it is approved for use in persons 6 months of age and older.

Meeting Date: Pediatric Advisory Committee Meeting, April 2023

Contents

1 INTRODUCTION

1.1 Objective

This memorandum for the Pediatric Advisory Committee (PAC) presents a comprehensive review of the postmarketing pediatric safety covering a period including 18 months following the approval in accordance with Section 505B (i) (1) of the Food and Drug Cosmetic Act [21 U.S.C. §355c]. On August 26, 2016, the FDA approved the Seqirus request to supplement the BLA for Influenza Vaccine (Afluria ®) to include a quadrivalent formulation (Afluria Quadrivalent) for use in persons 18 years of age and older. The triggers for this pediatric postmarketing safety review were the approvals of STNs:

- 125254/642 on August 31, 2017, to extend the indication for use to persons 5 years and older
- 125254/692 on October 4, 2018, to extend the indication for use to persons 6 through 59 months of age

This memorandum documents the Food and Drug Administration's (FDA's) complete evaluation, including review of adverse event (AE) reports in passive surveillance data, periodic safety reports from the manufacturer, data mining, and a review of the published literature.

1.2 Indication and Product Description

Afluria Quadrivalent is an inactivated influenza vaccine for intramuscular injection, indicated for active immunization against influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. Afluria Quadrivalent is approved for use in persons 6 months of age and older.[1]

Afluria Quadrivalent (hereby referred to as Afluria QIV) is prepared from influenza virus propagated in the allantoic fluid of embryonated chicken eggs. The vaccine is a suspension, to be administered via intramuscular injection, by needle and syringe (6 months and older) or by PharmaJet Stratis Needle-Free Injection System (18 through 64 years). Afluria QIV is currently supplied in two presentations – a 0.5 mL pre-filled syringe without a preservative, and a multi-dose vial containing ten 0.5 mL single doses containing thimerosal as a preservative.

Specific vaccine strain composition for all seasonal influenza vaccines is determined annually by the FDA's Vaccines and Related Biological Products Advisory Committee, taking into consideration recommendations from the World Health Organization. The Centers for Disease Control and Prevention (CDC) Advisory Committee on

[1] Afluria Quadrivalent U.S. package insert; updated July 1, 2022

Immunization Practices (ACIP) provides and periodically updates recommendations for use of seasonal influenza vaccinations.[2]

Trivalent vs. Quadrivalent Formulations of Seasonal Influenza Vaccines

Afluria QIV is manufactured using the same process as Afluria – a trivalent formulation (TIV). Trivalent (three-strain) influenza vaccines protect against the strains expected to be predominant in humans each year: two subtype A virus strains and a type B strain. Two influenza B virus lineage strains circulate to varying degrees each year making it difficult to predict which one will predominate in a particular influenza season. Quadrivalent (four-strain) influenza vaccine formulations are designed to protect against both influenza A subtypes and both influenza B strains, providing additional coverage.

1.3 Regulatory History

- August 26, 2016: Approval of STN 125254/565 to include a quadrivalent influenza virus vaccine formulation for use in persons 18 years and older
- August 31, 2017: Approval of STN 125254/642 to extend the indication for use to persons 5 years and older
- October 4, 2018: Approval of STN 125254/692 to extend the indication for use to persons 6 through 59 months of age

Approvals for STNs 125254/642 and 125254/692 serve as the regulatory triggers for the current PAC review.

2 MATERIALS REVIEWED

- Vaccine Adverse Events Reporting System (VAERS)
  - VAERS reports for Afluria QIV during August 31, 2017, to October 31, 2022 (PAC review period)
- Manufacturer's Submissions
  - Afluria QIV U.S. package insert; updated July 1, 2022
  - Applicant response to information request regarding dose distribution data under STN 125254/828
  - Pharmacovigilance Plan, Version 3.0, dated October 17, 2017
  - Periodic safety reports
- FDA Documents
  - STNs 125254/565, 125254/642, 125254/692 Afluria QIV approval letters
  - STN 125254/692 Pharmacovigilance Plan Review Memorandum
- Publications (see Literature Search in Section 7)
- IR response (BLA 125254/828) received December 05, 2022
- IR response (BLA 125254/828) received December 20, 2022

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

3 LABEL CHANGES IN REVIEW PERIOD

During the PAC review period, the following label changes were associated with postmarketing safety data:

- On March 4, 2021, a labeling supplement was approved under STN 125254/778 to revise the USPI to include postmarketing data specific to the quadrivalent formulation. Section 6.2 *Postmarketing Experience* of the USPI was updated to include the following adverse events (AEs): dizziness, musculoskeletal pain and pain in the extremity, injected limb mobility decreased, pyrexia, injection site erythema and injection site reaction, and another preferred term (PT) was revised from "vasculitis which may be associated with transient renal involvement" to "vasculitis which may be associated with renal involvement."
  In reference to the PT "vasculitis which may be associated with transient renal involvement", the removal of the word "transient" was proposed because the post-marketing case reports of vasculitis with renal involvement do not always contain sufficient information to confirm the duration of the renal manifestations (if any).
  The updates in Section 6.2 *Postmarketing Experience* of the USPI were the result of the analysis post marketing data cumulative to 15 March 2019.

4 PRODUCT UTILIZATION DATA

Seqirus provided estimated distribution data for Afluria QIV in the US and worldwide for the PAC review period:

Season(s)*	**Afluria QIV Doses Distributed (million doses)**		**TOTAL**
	US	**Rest of the World**	
NH17/18	10.43	1.34	11.77
SH18; NH18/19	17.80	1.56	19.36
SH19; NH19/20	19.98	3.19	23.17
SH20; NH20/21	21.40	7.10	28.50
SH21; NH21/22	13.78	7.70	21.48
SH22; NH22/23 (to date)	8.91	7.05	15.96
TOTAL	**92.30**	**27.94**	**120.24**

Abbreviations: NH= Northern Hemisphere; SH = Southern Hemisphere.

The sponsor was not able to provide data on proportion of doses distributed to pediatric and adult patients. Note that the number of doses distributed is an estimate of the number of patients vaccinated, because doses may have been distributed without being administered to patients, or 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), Version 3.0, dated October 17, 2017, lists the following important identified and potential risks, and missing information for Afluria QIV (see Table 1):

Table 1: Afluria QIV Safety Concerns

Important Identified Risks
Hypersensitivity (Anaphylaxis)
Important Potential Risks
Encephalomyelitis
Seizures/convulsions (including febrile)
Guillain-Barré syndrome
Transverse myelitis
Optic neuritis
Bell's palsy
Serum sickness
Large/extensive injection site swelling and cellulitis-like reactions
Missing Information
Exposure and safety in pregnancy

Hypersensitivity (Anaphylaxis): Allergic or immediate hypersensitivity reactions including anaphylactic shock is labeled in section *6.2 Postmarketing Experience*. Afluria QIV is contraindicated in individuals with known severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine including egg protein, or to a previous dose of any influenza vaccine (labeled in section 4 *Contraindications*). Preventing and Managing Allergic Reactions is also included under section 5 *Warnings and Precautions*.

Encephalomyelitis: As per the PVP, the clinical trial safety database did not have any reported cases of encephalomyelitis. Encephalomyelitis is labeled under section *6.2 Postmarketing Experience.*

Seizures/convulsions (including febrile): Febrile seizures were detected in young children in Western Australia in association with the trivalent formulation in 2010.[3, 4] Convulsions (including febrile seizures) is labeled under section *6.2 Postmarketing Experience.*

Guillain-Barré Syndrome: As per the PVP, the clinical trial safety database did not have any reported cases of GBS. Guillain-Barré Syndrome (GBS) is labeled in section 5 *Warnings and Precautions* and section *6.2 Postmarketing Experience.*
GBS was associated with use of an A/New Jersey 1976 influenza vaccine in anticipation of a swine influenza epidemic and is routinely listed in the label of influenza vaccines.[5]

Transverse myelitis: As per the PVP, the clinical trial safety database did not have any reported cases of transverse myelitis. Transverse myelitis has been reported in association with a nasal attenuated novel influenza A(H1N1) vaccine.[6] Transverse myelitis is labeled under section *6.2 Postmarketing Experience.*

Optic neuritis: As per the PVP, the clinical trial safety database did not have any reported cases of optic neuritis. Optic neuritis has been reported post-influenza Vaccination and is included as a potential risk.[7]

Bell's palsy: As per the PVP, Bell's palsy was not observed in the clinical trials for Afluria QIV. Bell's palsy has been associated with use of an E. coli heat-labile toxin-containing intranasal inactivated influenza vaccine, never licensed or distributed within the US, which was withdrawn from the market.[8] A subsequent, well-designed epidemiological study did not show an association with other inactivated influenza vaccines and the development of Bell's palsy.[9]

Serum sickness: As per the PVP the clinical trial safety database did not have any reported cases of serum sickness. Serum sickness is labeled under section *6.2 Postmarketing Experience.*

Large/extensive injection site swelling and cellulitis-like reactions: Cellulitis and large injection site swelling (*6.2 Postmarketing Experience) and* swelling (6.1 *Clinical Trials*

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[3] Armstrong PK, Dowse GK, Effler PV, et al. Epidemiological study of severe febrile reactions in young children in Western Australia caused by a 2010 trivalent inactivated influenza vaccine. BMJ 2011;1:e000016.
[4] Therapeutic Goods Administration. Seasonal flu vaccine: Overview of vaccine regulation and safety monitoring and investigation into adverse events following 2010 seasonal influenza vaccination in young children. Available: https://www.tga.gov.au/sites/default/files/alerts-medicine-seasonal-flu-101008.pdf
[5] 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.
[6] Akkad W, Salem B, Freeman JW, Huntington MK. Longitudinally Extensive Transverse Myelitis Following Vaccination With Nasal Attenuated Novel Influenza A(H1N1) Vaccine. Arch Neurol. 2010;67(8):1018–1020
[7] Solomon A, Siganos CS, Frucht-Pery J. Adverse ocular effects following influenza vaccination. Eye (Lond). 1999 Jun;13 (Pt 3a):381-2.
[8] Mutsch M, Zhou W, Rhodes P, et al. Use of the inactivated intranasal influenza vaccine and the risk of Bell's palsy in Switzerland. N Engl J Med 2004;350:896-903.
[9] Stowe J, Andrews N, Wise L, et al. Bell's palsy and parenteral inactivated influenza vaccine. Human Vaccines 2006;2:110-2.

Experience) are labeled events. This vaccine is administered via intramuscular injection, by needle and syringe (6 months and older) or by PharmaJet Stratis Needle-Free Injection System (18 through 64 years). The USPI includes clinical trial data on injection site reactions after administration by needle and syringe, and by the PharmaJet Stratis Needle-Free Injection System under section 6. *ADVERSE REACTIONS*.

The identified and potential risks listed in Table 1 are monitored with routine safety surveillance, including review of adverse event reports submitted to FDA, manufacturer submitted periodic safety reports, published literature, and data mining. There are no postmarketing requirement (PMR) safety-related studies under FDAAA or Risk Evaluation and Mitigation Strategy (REMS) for Afluria QIV. There is a pregnancy registry as a postmarketing commitment (PMC) study for pregnant women exposed to the quadrivalent formulation (please see section 5.2).

5.2 Postmarketing Studies

The following postmarketing studies were described in STN 125254/565 approval letter dated August 26, 2016.

Postmarketing requirements under Pediatric Research Equity Act (PREA)

- *Deferred pediatric study under PREA, to evaluate the immunogenicity and safety of Afluria® Quadrivalent in the pediatric population 5 through 17 years of age.*
- *Deferred pediatric study under PREA, to evaluate the immunogenicity and safety of Afluria Quadrivalent in the pediatric population 6 months through 4 years of age.*

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

Postmarketing commitment (PMC):

- *To establish a pregnancy registry to prospectively collect data on reported exposures to Afluria Quadrivalent during pregnancy and evaluate pregnancy outcomes. The registry will enroll a minimum of 500 evaluable subjects.*
    - Final Protocol Submission: September 30, 2017
    - *Study/Trial Completion Date: August 31, 2020**
    - *Final Report Submission: February 28, 2021*** **Revised to December 31, 2021; **Revised to July 31, 2022*

Study status: Final Study Report (FSR) submitted under STN 125254/820 and under ongoing FDA review.

6 ADVERSE EVENT REVIEW

6.1 Methods

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event reports following use of Afluria QIV received between August 31, 2017, and October 31, 2022 (PAC review period). VAERS stores postmarketing adverse events and medication errors submitted to FDA and CDC for all approved and authorized vaccines. These reports originate from a variety of sources, including healthcare providers, consumers, and manufacturers. Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in VAERS may not be medically confirmed and are not verified by FDA. FDA does not receive reports for every adverse event or medication error that occurs with a vaccine. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event. Also, there is no certainty that the reported event was due to the vaccine.

6.2 Results

The results of the VAERS search of AE reports for Afluria QIV during the PAC review period are listed in Table 2 below. There were 5,240 US and 250 foreign reports for the review period August 31, 2017, to October 31, 2022.

Table 2: Afluria QIV VAERS reports during August 31, 2017, to October 31, 2022

Age	Serious Non-Fatal*		Deaths		Non-Serious		Total Reported	
	US	Foreign	US	Foreign	US	Foreign	US	Foreign
<18 years	70	29	2	0	437	0	509	29
≥ 18 years	397	187	15	0	4011	0	4423	187
Unknown	95	33	0	0	213	1	308	34
All Ages	562	249	17	0	4661	1	5240	250

*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 17 deaths reported during the PAC review period, including 2 pediatric deaths. These reports were individually reviewed and are summarized below.

Pediatric death reports

- 13-year-old White male with history of Asperger's disorder, autism spectrum disorder, eustachian tube disorder, Raynaud's phenomenon and small intestinal obstruction. He was on treatment with Adderall and antidepressants (Fluoxetine).

One day after the vaccination, it is reported that, “he began acting differently”. He died of suicide 1 month after vaccination “despite seeming much happier & outgoing*”.*

- 11-month-old female with gastro-esophageal reflux disorder (GERD), who had been seen one week prior at the doctor’s office for viral URI, cough and earache, received Afluria Quadrivalent, Engerix-B, Infanrix, Hiberix, Pneumococcal vaccine (no brand name) and IPOL. Within 4 hours of vaccination, she became febrile and had seizures. The child died one month after vaccination. Autopsy report indicated that final cause of death as: asphyxia complicating hydroxyzine toxicity.

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

Adult death reports

There were 15 U.S. death reports in adults during the review period, including one duplicate report. Cases involved cardiovascular disease (n = 3, including 1 duplicate report); COVID-19 related deaths (n = 2), cause of death was undetermined (n= 3), narcotic related deaths (n = 2), absence seizure with limited clinical details (n = 1), respiratory failure and dementia (n = 1), acute asthma attack (n = 1), sudden death (n = 1), autoimmune hemolytic anemia and died of cardiorespiratory arrest (n = 1).

Reviewer comments: There were no reports of adult deaths that were attributed to Afluria QIV based on FDA review. Patients had underlying conditions and comorbidities that were contributing factors, and alternative etiologies were present.

6.2.2 Serious Non-fatal Reports

During the PAC review period, there were 811 serious non-fatal reports, including 99 pediatric reports and 584 adult reports. Age was unknown for the remaining 128 reports.

The most common Medical Dictionary for Regulatory Activities (MedDRA) PTs for pediatric reports are displayed in Table 3. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 3: Most frequently reported PTs for pediatric (< 18 years) serious non-fatal reports

Preferred Tern (PT)	# Serious Pediatric Reports	*Label Status (label section)
Syncope	17	Unlabeled
Pyrexia	14	Labeled (sections 6.1 and 6.2)
Seizure	10	Labeled (sections 6.1 and 6.2)
Vomiting	10	Labeled (section 6.1)
Loss Of Consciousness	8	Unlabeled

Preferred Tern (PT)	# Serious Pediatric Reports	*Label Status (label section)
Pallor	8	Unlabeled
Fall	7	Unlabeled
Condition Aggravated	6	Unlabeled
Nausea	6	Labeled (section 6.1)
Fatigue	5	Labeled (section 6 and 6.1)
Presyncope	5	Unlabeled
Tremor	5	Unlabeled

Note: PTs occurring with a frequency > 5 reports are shown in above table.
*Label approved July 1, 2022 (includes the 2022-2023 United States formulation and associated labeling revisions)

Reviewer comments: (b) (4)

"Syncope (and related terms, loss of consciousness, presyncope) can occur with any injectable product, and is most common among adolescents and young adults (https://www.cdc.gov/vaccinesafety/concerns/fainting.html). The term *loss of consciousness* is another term used to describe *syncope*. The PTs *pallor* and *condition aggravated* represent non-specific events that may occur in association with multiple conditions. *Falls* are common complaints in children, particularly children who are learning how to walk. A manual review of the reports of *tremor* indicated that this event developed in the context of seizures (n=3), anxiety (n=1) or syncope (n=1). All other PTs in table 3 are labeled events.

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

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

Preferred Tern (PT)	# Serious Adult Reports	*Label Status (label section)
Exposure during pregnancy	123	*Unlabeled*
Pain	93	Labeled (section 6 and 6.1)
Dyspnoea	75	*Unlabeled*
Nausea	74	Labeled (section 6.1)
Headache	71	Labeled (sections 6 and 6.1)
Hypoaesthesia	70	*Unlabeled*
Pain in extremity	69	Labeled (section 6.2)
Dizziness	65	Labeled (section 6.2)
Fatigue	63	Labeled (sections 6 and 6.1)
Pyrexia	62	Labeled (sections 6.1 and 6.2)

Preferred Tern (PT)	# Serious Adult Reports	*Label Status (label section)
Paraesthesia	55	Labeled (section 6.2)
Malaise	55	Labeled (sections 6 and 6.1)
Muscular weakness	51	*Unlabeled*
Asthenia	51	*Unlabeled*

Note: PTs occurring with a frequency >50 reports are shown in above table.
*Label approved July 1, 2022 (includes the 2022-2023 United States formulation and associated labeling revisions)

Reviewer comments: Most PTs are labeled events or consistent with an already labeled event. The PT *exposure during the pregnancy* does not represent a clinical adverse event. A manual review of the reports of *dyspnea* indicated that dyspnea developed mostly in the context of a hypersensitivity reaction (n=28), GBS/paralysis (n=8), myocarditis/pericarditis (n=5) and presyncope/syncope (n=3).

6.2.3 Non-serious Reports

During the reporting period, there were 4662 non-serious reports; 437 of which involved pediatric individuals. Table 5 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: Ten most frequently reported PTs in non-serious reports

Preferred Term (PT)	# Non-serious Reports	*Label Status *Label dated July 1, 2022 (Label Section)*
Pain	674	Labeled (section 6)
Injection site pain	563	Labeled (section 6)
Pain in extremity	559	Labeled (section 6.2)
Headache	549	Labeled (sections 6 and 6.1)
Pyrexia	549	Labeled (sections 6.1 and 6.2)
Chills	395	Labeled (section 6.1)
Nausea	390	Labeled (section 6.1)
Dizziness	376	Labeled (sections 6.2)
Fatigue	318	Labeled (sections 6 and 6.1)
Injection site erythema	315	Labeled (section 6.1 and 6.2)
Erythema	298	Labeled (section 6.1 and 6.2)
Rash	261	Labeled (section 6.1 and 6.2)
Injection Site Swelling	260	Labeled (section 6.1 and 6.2)
Pruritus	255	Labeled (section 6.2)
Urticaria	249	Labeled (section 6.2)
Myalgia	242	Labeled (sections 6 and 6.1)
Arthralgia	214	Unlabeled
Vomiting	214	Labeled (section 6.1)

Preferred Term (PT)	# Non-serious Reports	*Label Status *Label dated July 1, 2022 (Label Section)*
Dyspnoea	180	Unlabeled
Peripheral Swelling	179	Unlabeled

Reviewer comments: Most frequently reported PTs for non-serious reports were labeled events or PTs that can occur in the context of a variety of conditions in adult and pediatric populations.

6.3 Data mining

Data mining was performed to evaluate whether any reported events following the use of Afluria QIV were disproportionally reported compared to other vaccines in the VAERS database. The background database contains VAERS reports since 1990. Disproportionality alerts do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation. A query of Empirica Signals Management with the US VAERS Vac Name run with a data lock date of November 25, 2022, for INFLUENZA (SEASONAL) (AFLURIA QUADRIVALENT) identified the following unlabeled PTs discussed below, with a disproportional reporting alert (EB05>2; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean).

Table 6: Data mining findings

Preferred Term (PT)	# Reports	*Label Status *Label dated July 1, 2022 (Label Section)*
Joint range of motion decreased	109	*Unlabeled*
Ocular hyperemia	56	*Unlabeled*
Bursitis	43	*Unlabeled*

Reviewer comments: PTs for *joint range of motion decreased* and *bursitis* may represent adverse events of shoulder injury related to vaccine administration (SIRVA). This is caused by the injection of the vaccine into the shoulder capsule rather than the deltoid muscle. The key to preventing SIRVA and other vaccine injuries is correct injection technique and positioning[10]. A review of cases with PTs of *ocular hyperemia* indicated that all cases occurred in adults during the PAC review period with the exception one pediatric case. All events of ocular hyperemia were non-serious except one case where the subject required hospitalization in the context of GBS and another case where the subject developed an allergic reaction to the vaccine. Also, two subjects

[10] Shoemaker S. Preventing Shoulder Injury Related to Vaccine Administration. Am J Nurs. 2021 Jun 1;121(6):45-47

required an ER visit, in one case due to chest tightness, increased heart rate and blood pressure, in other case due to respiratory infection and conjunctivitis.

In addition to the above PTs, there were several PTs identified with disproportional reporting alerts involving pregnancy and pregnancy-related conditions. Most of the reports leading to these alerts were solicited reports identified and submitted via the sponsor's recently completed 500-patient pregnancy registry. In response to a request from FDA for information, Sequiris provided information on the pregnancy reports received for Afluria, both spontaneously and through the registry. More information on their response is below. Additionally, a published article describing the pregnancy registry results is discussed in Section 7.

Pregnancy-related PTs with disproportional reporting alerts included:

- PTs that represent conditions during pregnancy include *gestational diabetes; placenta previa; twin pregnancy; polyhydramnios; single umbilical artery*
- PTs that represent postpartum or obstetric procedures including *exposure during pregnancy; fetal exposure during pregnancy; delivery; Caesarean section; live birth*
- PTs that represent fetal complications include *large for dates baby; fetal growth restriction; low birth weight baby; premature baby; premature delivery*; *fetal disorder*
- PTs that represent laboratory tests/procedures and normal test results include *Apgar score normal*; *gene mutation identification test negative*; *ultrasound antenatal screen; alpha 1 foetoprotein normal; ultrasound antenatal screen; ultrasound antenatal screen normal*; *amniocentesis normal; prenatal screening test*
- PTs that represent abnormal results for laboratory tests/procedures include *Apgar score low; Apgar score abnormal; fetal gastrointestinal tract imaging abnormal; ultrasound antenatal screen abnormal, wrong technique in product usage process, beta haemolytic streptococcal infection*

Reports were reviewed and there were no patterns of AEs or data to suggest new safety concerns for Afluria QIV.

The reports for the PT, *ultrasound antenatal screen abnormal,* were further reviewed to screen for congenital malformations, and identified the specific ultrasonogram findings for gastroschisis (two cases) and lymphangioma. Both women who had a baby with gastroschisis / abdominal wall defect in fetus were vaccinated towards the end of the first trimester, at 8-11 weeks gestational age (GA). Most recent theories conclude that gastroschisis / abdominal wall defect in fetus is the result of rupture of the amniotic membrane at the base of the umbilical cord during either the time of normal "physiologic" umbilical herniation (5th through 10th weeks of fetal life) or at a later fetal stage in an embryo whose umbilical ring closure has been delayed. Of note, in one case the mother was 20 years old, and in the other case the mother had a UTI during the pregnancy. Young maternal age and UTI are both risk factors for gastroschisis.

Lymphangioma developed in a women who received Afluria QIV at 15.6 GA and the ultrasonogram revealed a congenital malformation of lymphangioma at 22 weeks GA however, lymphangiomas are typically diagnosed during the second and third trimester of the pregnancy.

In response to an FDA request for information on pregnancy-related reports, the sponsor provided a breakdown of pregnancy reports submitted to VAERS by source (received December 20, 2022, under 125254/828).

Cumulatively (from July 15, 2016 (IBD) to September 30, 2022), a total of 162 spontaneous reports involving potential exposure to Afluria QIV during pregnancy were received by Seqirus from worldwide sources (of which 76 were reported to VAERS). Of the 162 spontaneous reports, there were 157 'mother' cases and 5 'child' cases:

- ✓ Of the 157 'mother' cases, a total of 114 did not report any associated adverse events and pregnancy outcome was reported in only 16 cases including 10 live births, 5 spontaneous abortions and 1 fetal demise. In the case of fetal demise, the subject received Afluria QIV and Adacel at an unknown gestational age on October 6, 2022. On an unspecified date in Oct 2018, the subject was hospitalized and subsequently, was diagnosed with an intrauterine fetal death. The Kleihauer-Betke test resulted positive at the time of delivery (indicating fetal-maternal-hemorrhage) and no apparent congenital anomalies were reported.
- ✓ The 5 'child' cases included one case each of: mild form of hypospadias, cleft palate, premature / low birth weight baby, jaundice neonatal and foetal hypokinesia.

There were also 241 US solicited reports, originating from the Afluria QIV pregnancy registry (128 'mother cases' and 113 'child cases'), which were also reported to VAERS.

The sponsor concluded that the review of the cases from the pregnancy registry and spontaneous reports did not identify any safety concerns with the use of Afluria QIV during the pregnancy. DPV agrees with sponsor's assessment.

6.4 Periodic safety reports

The manufacturer's postmarketing periodic safety reports for Afluria 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 12/4/2022 for peer-reviewed literature, with the search term "Afluria Quadrivalent" and "safety" limited by human species, and dates from PAC trigger (August 31, 2017) to date of search 12/4/2022, retrieved 3 publications pertaining to safety. No new safety concerns

for Afluria QIV were identified in the review of these publications, summarized in the table below:

Publication	Authors' Safety Conclusion
Statler VA, Albano FR, Airey J, Sawlwin DC, Graves Jones A, Matassa V, Heijnen E, Edelman J, Marshall GS. *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	S-IIV4 (Afluria® Quadrivalent/Afluria Quad™/Afluria Tetra™, Seqirus Pty Ltd) manufactured with a higher detergent concentration, demonstrated noninferior immunogenicity to the US-licensed C-IIV4, with similar postvaccination safety and tolerability, in children aged 6–59 months.
Forster AH, Witham K, Depelsenaire ACI, Veitch M, Wells JW, Wheatley A, Pryor M, Lickliter JD, Francis B, Rockman S, Bodle J, Treasure P, Hickling J, Fernando GJP. *Safety, tolerability, and immunogenicity of influenza vaccination with a high-density microarray patch: Results from a randomized, controlled phase I clinical trial*. PLoS Med. 2020 Mar 17;17(3):e1003024	The study was a randomized, partially blinded, placebo-controlled phase I clinical trial. The trial aimed to assess safety / tolerability and immunogenicity of vaccination delivered by High density microarray patch (HD-MAP) where microprojections were coated with vaccine for delivery into the skin of 15 µg of A/Singapore/GP1908/ 2015 H1N1 (A/Sing) monovalent). Comparison groups included: uncoated MAP, IM injection of commercially available Afluria QIV containing A/Singapore/GP1908/2015 H1N1 HA (15 µg/dose) and IM injection of H1N1 HA antigen (15 µg/dose). Vaccination using the HD-MAP was safe and well tolerated and resulted in immune responses that were similar to or significantly enhanced compared with IM injection
Robinson C, Oberye J, van Boxmeer J, Albano JD, Tilson H, Scialli A, Vanchiere JA, Ides E, Sawlwin D, Hohenboken M, Edelman J. A *Prospective Cohort Study on Pregnancy Outcomes of Persons Immunized with a Seasonal Quadrivalent Inactivated Influenza Vaccine during Pregnancy*. Vaccines (Basel). 2022 Sep 21;10(10):1577	This US-based, prospective observational cohort study evaluated the safety of Afluria Quadrivalent) in pregnancy (Pregnancy registry, protocol CSLCT-OBS-17-15). Subjects were immunized over four influenza seasons between 2017 and 2021. Pregnancy outcomes included live birth, stillbirth, spontaneous abortion, and elective termination. Infant events of interest were major congenital malformations (MCMs), preterm birth, and low birth weight (LBW). A total of 483 pregnant persons were vaccinated and evaluated; 477 (98.8%) reported a live birth, and there were 2 stillbirths, 4 spontaneous abortions, and no elective terminations or maternal deaths. The prevalence rates of infant events were as follows: preterm birth, 7.2% (upper 95% CI, 9.6%); LBW, 5.4% (upper 95% CI, 7.4%); and MCMs, 0.8% (upper 95% CI, 1.9%). Point estimates and upper 95% CIs of the observed prevalence rates were lower than or similar to background prevalence

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	in the general US population. The study findings suggest no evidence of a safety concern with vaccination in pregnancy and are consistent with published data from databases and surveillance systems that monitor the safety of influenza vaccines in pregnancy.

8 CONCLUSION

This postmarketing pediatric safety review was triggered by the approvals of STNs:

- 125254/642 on August 31, 2017, to extend the indication for use of Afluria QIV in persons 5 years and older
- 125254/692 on October 4, 2018, to extend the indication for use of Afluria QIV to persons 6 through 59 months of age

Review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for Afluria QIV does not indicate any new safety concerns. Adverse events were generally consistent with the safety data in pre-licensure studies and listed in the label. No unusual frequency, clusters, or other trends for adverse events were identified that would suggest a new safety concern.

9 RECOMMENDATIONS

FDA recommends continued routine safety monitoring of Afluria Quadrivalent.