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 Pharmacovigilance (OBPV) Center for Biologics Evaluation and Research (CBER)
From:	Bethany Baer, MD Medical Officer, Pharmacovigilance Branch 1 (PB1) Division of Pharmacovigilance (DPV), OBPV, CBER Meghna Alimchandani, MD Deputy Director, DPV, OBPV, CBER
Subject:	Safety and Utilization Review for the Pediatric Advisory Committee
Applicant:	Seqirus Inc.
Product:	Agriflu (Influenza Virus Vaccine)
STN:	125297/140
Indication:	Agriflu is a vaccine indicated for the active immunization for the prevention of disease caused by influenza virus subtypes A and type B contained in the vaccine. Agriflu is approved for use in persons 18 years of age and older.
Meeting Date:	Pediatric Advisory Committee Meeting, 2024

Contents

1 INTRODUCTION

1.1 Objective

This memorandum for the Pediatric Advisory Committee (PAC) presents a comprehensive review of the postmarketing pediatric safety covering a period including 18 months following the approval in accordance with Section 505B (i) (1) of the Food and Drug Cosmetic Act [21 U.S.C. §355c]. The trigger for this pediatric postmarketing safety review for Agriflu was the approval of the supplemental Biologics License Application (sBLA) 125297/118 on January 28, 2020, to include data from three post-approval requirement/commitment studies conducted in pediatric and adult populations. Agriflu is approved for use in persons 18 years of age and older. As described in the Agriflu U.S. prescribing information (USPI), section 8.4 Pediatric Use:

> *Safety and effectiveness of Agriflu were evaluated in two clinical trials conducted in children and adolescents 6 months through 17 years of age. Data from these trials are inconclusive to establish the effectiveness of the vaccine in this population. The safety and effectiveness of Agriflu in infants less than 6 months of age have not been evaluated.*

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

Agriflu is indicated for the active immunization for the prevention of disease caused by influenza virus subtypes A and type B contained in the vaccine. Agriflu is approved for use in persons 18 years of age and older.[1]

Agriflu is a trivalent inactivated influenza virus vaccine prepared from virus propagated in the allantoic cavity of embryonated hens' eggs inoculated with an influenza virus suspension containing kanamycin and neomycin sulphate. Agriflu is a sterile clear aqueous suspension for intramuscular injection that is supplied in two presentations: 0.5 mL single-dose pre-filled syringes, and 5.0 mL multi-dose vial containing 10 doses (each dose is 0.5 mL). The 0.5 mL pre-filled syringe presentation is manufactured and formulated without thimerosal or any other preservative. The 5.0 mL multi-dose vial presentation contains thimerosal, a mercury derivative, added as a preservative. Each 0.5 mL dose from the multi-dose vial contains 25 mcg mercury.

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] Agriflu U.S. prescribing information, updated 01/2020

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

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

- October 1986: International Birthdate in Italy, approved under the name Agrippal.
- November 27, 2009: STN 125297/0 initial U.S. approval of Agriflu (0.5 mL preservative-free single dose syringes) under the accelerated approval regulations, for active immunization of adults 18 years of age and older against influenza disease caused by influenza virus subtypes A and type B present in the vaccine.
- October 29, 2010: STN 125297/1 traditional approval of Agriflu to include data from the confirmatory clinical studies to verify and describe the clinical benefit.
- 2010/2011 influenza season: Last distribution of Agriflu in the U.S.
- October 21, 2013: STN 125297/37 approval of Agriflu to include a multi-dose vial (MDV) presentation.
- February 2016: Marketing Authorization Holder of the Agriflu license changed from Novartis Vaccines and Diagnostics, Inc. to Seqirus.
- July 10, 2018: Seqirus notified FDA that they have discontinued distribution of Agriflu in the U.S.
- January 28, 2020: STN 125297/118 approval of Agriflu to include data from three postapproval requirement/commitment studies conducted in pediatric and adult populations.
    - Regulatory trigger for current PAC review

2 MATERIALS REVIEWED

- Vaccine Adverse Events Reporting System (VAERS)

[2] Grohskopf LA, Blanton LH, Ferdinands JM, Chung JR, Broder KR, Talbot HK. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023–24 Influenza Season. MMWR Recomm Rep 2023;72(No. RR-2):1–25. DOI: http://dx.doi.org/10.15585/mmwr.rr7202a1

    - VAERS reports for Agriflu during January 28, 2020 to October 31, 2023 (safety review period)
- Manufacturer's Submissions
    - Agriflu U.S. package insert; updated 01/2020
    - Applicant responses to information requests regarding dose distribution data, received under STN 125297/140
    - Pharmacovigilance Plan (Risk Management Plan and Appendix of Pharmacovigilance System dated June 22, 2008)
    - Product Correspondence: Permanent Discontinuation of Agriflu, July 10, 2018, under STN 125297/109
    - Periodic safety reports
- FDA Documents
    - Pharmacovigilance plan review memorandum under STN 125297/0
    - Review memo under STN 125297/121 for release of pregnancy registry postmarketing commitment
- Publications (see Literature Search in Section 7)

3 LABEL CHANGES IN REVIEW PERIOD

There were no safety related label changes during the review period January 28, 2020 to October 31, 2023.

4 PRODUCT UTILIZATION DATA

Seqirus Inc. confirmed that there was no U.S. distribution of Agriflu during January 28, 2020, to May 31, 2023. Agriflu has not been distributed in the U.S. since the 2010/2011 influenza season.

Outside the U.S., Agriflu is sold under the trade names Agriflu, Agrippal, Agrippal S1, Agrippal S1 Junior, Chiroflu, Viraflu and Viraflu Pediatrica. The sponsor estimates that, "approximately [redacted] individuals have been vaccinated with Agriflu and related trade names in the rest of the world (ROW) between 28 January 2020 to 31 May 2023." Pediatric exposure was estimated to vary from [redacted] of total doses distributed.

Table 1: Agriflu, Agrippal, Agrippal S1, Chiroflu, Viraflu, and Viraflu Pediatrica Doses Distributed Worldwide

Year (Seasons*)	Estimated Agriflu ROW adult doses distributed	Estimated Agriflu ROW pediatric doses distributed (% Total doses distributed)	Total
2020 (SH20; NH20/21)	(b) (4)	(b) (4)	(b) (4)
2021 (SH21; NH21/22)	(b) (4)	(b) (4)	(b) (4)
2022 (SH22; NH22/23)	(b) (4)	(b) (4)	(b) (4)
2023 (SH23)	(b) (4)	(b) (4)	(b) (4)
TOTAL	(b) (4)	(b) (4)	(b) (4)

*Abbreviations: NH=Northern Hemisphere; SH=Southern Hemisphere; ROW=Rest of the World

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. Distribution data is protected as confidential commercial information and may require redaction from this review.

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan

The manufacturer's current U.S. Pharmacovigilance Plan (Risk Management Plan [RMP] dated June 22, 2008), lists the following important potential risks and missing information for Agriflu (see Table 2). There are no important identified risks in the RMP.

Table 2: Agriflu Safety Concerns

Important Potential Risks
Guillain-Barré Syndrome (GBS)
Anaphylaxis including anaphylactic shock
Acute disseminated encephalomyelitis (ADEM)
Thrombocytopenia
Vasculitis
Neuritis of peripheral or cranial nerves
Missing Information
Children and adolescents
Pregnant or lactating women
Patients with relevant co-morbidities
Immune-compromised patients

The important potential risks were listed as "events of special interest" in the sponsor's Risk Management Plan (RMP). The RMP grouped Guillain-Barré Syndrome (GBS), anaphylactic reaction, Acute disseminated encephalomyelitis (ADEM), vasculitis, and

transient thrombocytopenia as Type B reactions that are mainly attributable to the susceptibility of the patient. Per the RMP, none of those reactions were seen during the clinical trials.

Guillain-Barré Syndrome (GBS): GBS is labeled under section 5 *Warnings and Precautions*, section 6.3 *Postmarketing Experience,* and section 6.4 *Adverse events after influenza vaccines* in the current Agriflu PI (1/2020).

*Anaphylaxis including anaphylactic shoc*k: At the time of the RMP, the sponsor had received spontaneous reports of anaphylactic reactions but no confirmed IgE-mediated cases of anaphylaxis for Agriflu. The current Agriflu PI includes preventing and managing allergic reactions under section 5 *Warnings and Precautions* and hypersensitivity reactions (including throat and/or mouth edema, anaphylaxis, and anaphylactic shock) under section 6.3 *Postmarketing Experience*.

Myelitis (including encephalomyelitis and transverse myelitis), Thrombocytopenia, Vasculitis (in rare cases associated with transient renal involvement), and Neuropathy (including neuritis and brachial plexus neuropathy) are listed under section 6.3 *Postmarketing Experience*.

The potential risks listed in Table 2 are monitored with routine safety surveillance by the manufacturer, including review of safety reports, use of signal detection tools, and submission of periodic safety reports. In years that the product was distributed in the U.S., the FDA's routine surveillance included review of adverse event reports submitted to FDA, manufacturer submitted periodic safety reports, published literature, and data mining. When there has been no distribution in the U.S., FDA's surveillance includes reviewing the manufacturer's submitted periodic safety reports. There are no postmarketing requirement (PMR) safety-related studies under FDAAA or Risk Evaluation and Mitigation Strategy (REMS) for Agriflu. The sponsor has been released from a postmarketing commitment (PMC) for a pregnancy registry because the study was infeasible given the discontinuation of U.S. distribution for Agriflu (please see section 5.2).

5.2 Postmarketing Studies

The following postmarketing studies were described in STN 125297/0 approval letter dated November 27, 2009:

Postmarketing requirement (PMR) under accelerated approval:

- "Novartis Vaccines and Diagnostics agrees to submit the results of Study No. V58P13, a placebo-controlled clinical endpoint efficacy and safety study of Novartis's AGRIFLU in healthy adults 18 to 49 years of age. The final study report for the study will be submitted by January 31, 2010."
  Study status: Fulfilled

PMRs under Pediatric Research Equity Act (PREA):

- “Novartis Vaccines and Diagnostics agrees to conduct Study No. V71_18, a randomized, observer-blind, non-inferiority immunogenicity and safety study with Novartis’s AGRIFLU and a US-licensed trivalent inactivated Influenza Vaccine in a pediatric population from 3 years to 17 years of age.”
  Study status: Fulfilled
- “Novartis Vaccines and Diagnostics agrees to conduct Study No. V71_20, a randomized, observer-blind, immunogenicity and safety study with Novartis’s AGRIFLU and a US-licensed trivalent inactivated Influenza Vaccine in a pediatric population from 6 months to less than 3 years of age.”
  Study status: Fulfilled

Postmarketing commitments (PMCs):

- “Novartis Vaccines and Diagnostics agrees to establish a pregnancy registry to prospectively collect data on spontaneously reported exposures to AGRIFLU during pregnancy.”
  Study status: Released (125297/121 release letter dated August 5, 2020) because the study was no longer feasible as U.S. distribution of Agriflu was discontinued after the 2010/2011 season.

- “Novartis Vaccines and Diagnostics agrees to conduct a non-inferiority immunogenicity study with AGRIFLU and a US-licensed trivalent inactivated seasonal influenza vaccine in a population of adults 50 years of age and older.”
  Study status: Fulfilled

6 ADVERSE EVENT REVIEW

6.1 Methods

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event reports following use of Agriflu between January 28, 2020, to October 31, 2023 (safety review period). VAERS stores postmarketing adverse events and medication errors submitted to FDA and CDC for all approved vaccines. These reports originate from a variety of sources, including healthcare providers, consumers, and manufacturers. Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, variable report quality and accuracy, inadequate data regarding the number 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 Agriflu during the PAC review period are listed in Table 3 below. There was 1 US and 3 foreign reports for the review period January 28, 2020, to October 31, 2023.

Table 3: Agriflu VAERS reports during January 28, 2020, to October 31, 2023

Age	Serious, Non-Fatal* US	Serious, Non-Fatal* Foreign	Deaths US	Deaths Foreign	Non-Serious US	Non-Serious Foreign	Total Reported US	Total Reported Foreign
<18 years	0	1	0	0	0	0	0	1
≥ 18 years	0	2	0	0	1	0	1	2
Unknown	0	0	0	0	0	0	0	0
All Ages	0	3	0	0	1	0	1	3

*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 no deaths reported during the PAC review period.

6.2.2 Serious Non-fatal Reports

During the PAC review period, there were 3 serious non-fatal reports, including 1 pediatric report and 2 adult reports.

The MedDRA preferred terms (PTs) for the pediatric report are displayed in Table 4. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

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

Preferred Term (PT)	# Serious Pediatric Reports	*Label Status *Label dated Jan 2020 (Label Section)*
Malaise	1	Labeled (sections 6.1, 6.2, 6.3)
Pyrexia	1	Labeled as fever (sections 6.2, 6.3)
Vomiting	1	Labeled (section 6.3)

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Reviewer comments: The single pediatric case was a 10-year-old boy who had malaise, pyrexia, and vomiting at an unknown time after receiving Agriflu. The pharmacist who reported the event marked it as an otherwise medically important condition (OMIC). The patient was not hospitalized. All of the associated PTs are labeled for Agriflu.

The PTs for adult reports are displayed in Table 5. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 5: Reported PTs for adult serious non-fatal reports

Preferred Term (PT)	# Serious Adult Reports	*Label Status
Asthenia	1	Labeled (section 6.3)
Disability	1	Unlabeled
Headache	1	Labeled (sections 6.1, 6.2, 6.3)
Hypokinesia	1	Unlabeled
Influenza Like Illness	1	Labeled (section 6.2)
Loss of Personal Independence in Daily Activities	1	Unlabeled
Malaise	1	Labeled (sections 6.1. 6.2, 6.3)
Pain in Extremity	1	Labeled as pain and injection site pain (sections 6.1, 6.2, 6.3)
Pyrexia	1	Labeled as fever (sections 6.2, 6.3)

Reviewer comments: *There were 2 reports that contributed the PTs to Table 5 above. Most of the PTs were labeled events. The report that contained the 3 unlabeled PTs was a report of a 39-year-old female who developed hypokinesia, pain in extremity, and loss of personal independence in daily activities at an unspecified time after receiving Agriflu. The patient had not recovered at the time of the report, and the PT of disability was also connected with this case.* While disability, hypokinesia, and loss of personal independence in daily activities are unlabeled, the Agriflu package insert does include pain limiting limb movement and extensive swelling of injected limb lasting more than one week in section 6.3. As this case also involved the PT of pain in extremity, the other unlabeled PTs may be associated with the labeled event of pain limiting limb movement.

6.2.3 Non-serious Reports

During the reporting period, there was 1 non-serious report, which involved an adult. Table 6 below lists the reported PTs in the non-serious report. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 6: Reported PTs in non-serious reports

Preferred Term (PT)	# Non-serious Reports	Label Status
Expired Product Administered	1	Not an adverse event
No Adverse Event	1	Not an adverse event

Reviewer comments: *The single non-serious case occurred in a 27-year-old female in the U.S. who received a Covid-19 vaccine which was expired. There was no clinical adverse event. The report listed Agriflu as a concomitant vaccine, but since the report was from the U.S. during a time when Agriflu had not been distributed for many years, the reporting of Agriflu as the concomitant vaccine was likely an error.*

6.3 Data mining

Data mining was performed to evaluate whether any reported events following the use of Agriflu 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 as of Dec. 15, 2023, for INFLUENZA (SEASONAL) [Agriflu] did not identify any PTs 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).

Reviewer comments: There have been few reports in VAERS for Agriflu, likely due to its limited time of distribution in the U.S. The reports that were received did not show any disproportionality compared to the background of vaccine reports in VAERS.

6.4 Periodic safety reports

The manufacturer's postmarketing periodic safety reports for Agriflu were reviewed. The AEs reported were consistent with the known safety profile.

The most recent Periodic Safety Update Report (PSUR)[3] references the EU RMP from 2017 that has updated anaphylactic reactions to the important identified risk category. The EU RMP also includes Bell's palsy, convulsion, demyelination, and vaccination failure as important potential risks. This PSUR includes surveillance on all of the important risks for the period of March 16, 2022 – March 15, 2023. The PSUR reports that there has been 1 case of encephalitis in a patient known to have received Agrippal during the 1-year period. All of the other risks listed had reports of events after international non-proprietary name influenza vaccines only; there were no other reports of Agrippal-confirmed events for that period in the sponsor's postmarketing database.

Reviewer comment: The label includes a subsection titled "Preventing and Managing Allergic Reactions" under Warnings and Precautions section of the USPI. Bell's Palsy, convulsion, Guillain-Barré Syndrome, myelitis (including encephalomyelitis and transverse myelitis) are labeled events (Postmarketing Experience section of USPI) and discussed in section 5.1 Pharmacovigilance Plan of this memorandum. Information describing Limitations of Vaccine Effectiveness under Warnings and Precautions section of the USPI, states that, "Vaccination with AGRIFLU may not protect all recipients."

7 LITERATURE REVIEW

A search of the US National Library of Medicine's PubMed.gov database on Dec. 20, 2023, for peer-reviewed literature, with the search term "Agriflu" and "safety" limited by human species, and dates from PAC trigger (January 28, 2020) to date of search (Dec.

[3] Periodic Safety Update Report for Agrippal for the dates of Mar 16, 2022 to Mar 15, 2023, submitted as 125297/141.

20, 2023) retrieved 2 publications pertaining to safety. No new safety concerns for Agriflu were identified in the review of these publications, summarized in the table below:

Publication	Authors' Safety Conclusion
Munoz FM, Patel SM, Jackson LA, et al. Safety and immunogenicity of three seasonal inactivated influenza vaccines among pregnant women and antibody persistence in their infants. Vaccine. 2020 Jul 14;38(33):5355-5363.	The study enrolled 139 pregnant women and 44 non-pregnant women and randomized the subjects to receive one of three licensed trivalent inactivated vaccines (Agriflu, Fluzone, or Fluarix) prior to 2010-2011 influenza season. There were similar frequencies of injection site and systemic reactions between pregnant and non-pregnant women. There were no vaccine-associated maternal or infant serious adverse events. The authors concluded that the 3 trivalent inactivated flu vaccines were well tolerated in pregnant women.
Influenza Vaccine for 2020-2021. The Medical Letter on Drugs and Therapeutics. 2020 Sep 21;62(1607);145-150.	This review article discusses the types of influenza vaccines and brand names available for the 2020-2021 season. Agriflu was listed as a keyword for the article but did not appear in the article. Agriflu was not on the article's list of U.S.-available 2020-21 seasonal influenza vaccines.

8 CONCLUSION

This postmarketing pediatric safety review was triggered by the approval of sBLA 125297/118 on January 28, 2020, to include data from three post-approval requirement/commitment studies conducted in pediatric and adult populations. In the U.S., Agriflu is approved for use in persons 18 years of age and older. Review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for Agriflu 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. U.S. distribution of Agriflu has been discontinued since the 2010/2011 influenza season.

9 RECOMMENDATIONS

FDA recommends continued routine safety monitoring for Agriflu.