Summary Basis for Regulatory Action

Date: 29 August 2017

From: Timothy A. Fritz, Review Committee Chair

BLA STN#: 125254/642

Applicant Name: Seqirus Pty. Ltd.

Date of Submission: 28 October 2016

Goal Date: 31 August 2017

Proprietary Name/ Established Name: Afluria® Quadrivalent

Indication: Afluria Quadrivalent is currently indicated for the prevention of influenza disease in persons 18 years of age and older caused by influenza virus subtypes A and types B contained in the vaccine. This supplement is intended to include safety and effectiveness data to support the use of Afluria Quadrivalent in persons 5 through 17 years of age.

Recommended Action:
The Review Committee recommends approval of this product.

Review Office Signatory Authority: Wellington Sun, MD, Director, Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review

☒ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

The table below indicates the material reviewed when developing the SBRA

Document title	**Reviewer name, Document date**
Clinical Reviews • *Clinical (OVRR/DVRPA)* • *Postmarketing safety epidemiological review (OBE/DE)* • *Bioresearch Monitoring (OCBQ/DIS)*	Cynthia Nolletti, MD—28 August 2017 Wenyu Sun, MD—29 May 2017 Carla Jordan—15 June 2017
Statistical Reviews	

• *Clinical data (OBE/DB)*	Charles (Yin Kiu) Cheung, PhD—15 June 2017
CMC Review • *CMC (OVRR/DVP)*	Falko Schmeisser, PhD—11 August 2017
Labeling Reviews • *OVRR/DVRPA* • *OVRR/DVRPA*	Daphne Stewart—18 August 2017 Helen Gemignani—01 August 2017
Other Review • *APLB labeling consult review (OCBQ/APLB)*	Sonny Saini, PharmD—21 March 2017

1. INTRODUCTION

Seasonal epidemics caused by influenza virus infection are a significant source of hospitalization and death in the U.S. and throughout the world. The young (persons < 5 years of age), elderly (persons > 65 years of age) and those with certain underlying medical conditions are the most severely affected by these epidemics. In humans, influenza subtype A and type B viruses are responsible for seasonal influenza illness and annual vaccination is the most effective means to reduce the risk of disease caused by influenza virus infection.

Afluria® Quadrivalent is a vaccine manufactured by Seqirus Pty Ltd (Seqirus) indicated for the active immunization of persons 18 years and older for the prevention of influenza disease caused by influenza virus subtypes A and types B contained in the vaccine. Afluria Quadrivalent is formulated as a sterile, aqueous, buffered suspension of four egg-grown, inactivated influenza viruses for intramuscular injection. Each 0.5 mL dose of the vaccine contains 60 mcg of viral hemagglutinin (15 mcg each of H1N1, H3N2, B/Victoria and B/Yamagata hemagglutinins), and is available in single dose, pre-filled syringes without thimerosal or in a multidose vial presentation which contains thimerosal as a preservative. Compared to Seqirus' Afluria® trivalent influenza vaccine, Afluria Quadrivalent contains an additional type B influenza virus antigen. The inclusion of two B-type virus antigens in quadrivalent influenza vaccines is intended to provide protection against both B/Yamagata and B/Victoria lineage influenza viruses. This is particularly important for pediatric populations because type B influenza infection is common and frequently severe in children and there is little to no cross protection offered by one type B vaccine antigen against type B viruses of the other lineage.

CBER received supplement STN 125254/642 on 28 October 2016 with efficacy, immunogenicity and safety data from a single study (CSLCT-QIV-13-02) of Afluria Quadrivalent conducted in children and adolescents 5 through 17 years of age. The supplement was submitted to fulfill one of two postmarketing studies required by the Pediatric Research Equity Act (PREA) and to extend the Afluria Quadrivalent indication to persons 5 through 17 years of age.

2. BACKGROUND

Afluria (trivalent formulation) was licensed in the U.S. for persons 18 years of age and older on 28 September 2007 (STN 125254/0). The license was issued under accelerated approval conditions to CSL Biotherapies, Seqirus' former corporate name. Licensure under accelerated approval was extended to persons 6 months through 17 years of age on 10 November 2009 with the approval of supplement STN 125254/132. Confirmation of clinical benefit in persons 18 years and older to fulfill the accelerated approval requirement was submitted in supplement STN 125254/259, which was approved on 02 December 2011. This supplement also contained the results from two postmarketing commitment immunogenicity and safety studies in children 6 months through 17 years of age. Results from a clinical trial supporting the administration of Afluria to persons 18 through 64 years using the PhamaJet® Stratis® Needle-free Injection System were submitted under supplement STN 125254/511 which was approved on 15 August 2014. Afluria Quadrivalent was approved for use in adults 18 years and older on 26 August 2016 (STN 125254/565) based upon results from a non-inferior immunogenicity and safety study (CSLCT-QIV-13-01).

During the 2010 Southern Hemisphere influenza season, Fluvax® and Fluvax® Junior (the proprietary names of the Afluria formulations used in the Southern Hemisphere) were associated with an increased risk for pediatric febrile seizures, predominantly in children < 5 years of age. As a result, a warning was included in the Afluria package insert for the 2010-2011 U.S. influenza season, and the U.S. Advisory Committee on Immunization Practices (ACIP) recommended that the 2010-2011 Afluria vaccine not be administered to children aged 6 months through 8 years of age. On 15 July 2011, FDA restricted the use of Afluria to persons ≥ 5 years of age (STN 125254/303).

Seqirus conducted a root cause investigation of the febrile seizures and identified vaccine viral RNA and lipid content as potential contributors to the increase in febrile seizures. Seqirus (b) (4) in an effort to reduce the reactogenicity of Afluria. To assess the impact of this manufacturing change on vaccine safety, Seqirus completed a postmarketing safety and tolerability study (CSLCT-USF-10-69) in children 5 to < 9 years old of Afluria (trivalent formulation) manufactured with the revised procedures. The study was conducted in a pediatric population for which febrile seizures are less common prior to proceding with additional studies in children < 5 years of age who are at greater risk for such seizures. The primary endpoint of study CSLCT-USF-10-69 was to assess the frequency and intensity of fever within 7 days of Afluria administration. A secondary study endpoint assessed the frequency and intensity of fever within 7 days following administration of a U.S.-licensed, quadrivalent influenza vaccine comparator. Direct comparison between the two vaccines could not be made as the study was not sufficiently powered to assess differences but the results showed that the rates of fever observed for each vaccine were comparable and served as a basis to support the Phase 3 study CSLCT-QIV-13-02.

Seqirus identified an increase in reports of cellulitis and large injection site swelling during its 2011 review of its worldwide safety database. Based upon their analysis of the

data, Seqirus submitted a supplement (STN 125254/440) to include cellulitis and large injection site swelling in the *Postmarketing Experience* section of the Afluria package insert. The labeling change was approved on 04 April 2013.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

a) Product Quality

The manufacture of monovalent bulk Drug Substance used to formulate Afluria Quadrivalent uses the same process as that approved for the manufacture of the Afluria trivalent formulation of (STN 125254/0). The formulation and filling process for Afluria Quadrivalent was reviewed and approved on 26 August 2016 under STN 125254/565.

HI assay validation reports were provided for the four vaccine antigens used in study CSLCT-QIV-13-02. Reports for two of the antigens [A/California/7/2009 (H1N1) and B/Brisbane/60/2008] were previously reviewed and approved under STN 125254/565. The HI validation reports for the remaining two antigens [A/South Australia/55/2014 (H3N2) and B/Phuket/3073/2013] were reviewed by the Product Reviewer and are acceptable.

b) CBER Lot Release

There were no pending lots or issues that would affect approval of this supplement.

c) Facilities review/inspection

There were no ongoing or pending investigations or compliance actions that would affect approval of this supplement.

d) Environmental Assessment

The supplement included a request for a categorical exclusion for an environmental assessment under 21 CFR 25.31 (c). The FDA concluded that this request is justified as the manufacture of Afluria Quadrivalent will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

e) Product Comparability

N/A

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

A reproductive toxicity study of Afluria (trivalent formulation) was conducted in rats using full human doses and was reviewed under STN 125254/124. All mating and

fertility parameters were comparable between control and vaccine groups. No malformations (skeletal and visceral) and no developmental effects caused by and associated with the vaccine were observed. Nonclinical pharmacology/toxicology data were not provided in this supplement because CBER advised Seqirus under IND 15974 that this data would not be needed due to the similarity of Afluria Quadrivalent to Afluria (trivalent formulation).

5. CLINICAL PHARMACOLOGY

The distribution of demographic and baseline characteristics of the 2278 subjects in the Full Analysis Set (FAS) population was similar between treatment groups. Overall, there were more male (52.1%) than female (47.9%) subjects. The majority of subjects were white (73.3%) and non-Hispanic or Latino (76.0%). Black/African American and Hispanic/Latino subjects comprised 20.7% and 23.8% of the FAS, respectively. American Indian/Alaskan Native (0.3%), Asian (0.8%), Native Hawaiian/Pacific Islander (0.7%), and racial groups identified as "other"(4.3%) comprised the remainder of the FAS. Demographic and baseline characteristics within each age cohort were similar to the FAS and between treatment groups. Relative to the U.S. population, blacks/African Americans and Hispanics/Latinos were overrepresented, and Asians were underrepresented.

The mean age (standard deviation) of all subjects in the FAS was 9.5 (3.48) years; 6.7 (1.10) for the 5-8 year age cohort; and 12.5 (2.52) for the 9-17 year age cohort. As specified by the protocol, at least 50% of subjects in the FAS (51.2%) were in the 5-8 years cohort.

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

Study CSLCT-QIV-13-02

Study CSLCT-QIV-13-02 was a Phase 3, randomized, multicenter, observer-blinded, noninferiority study conducted in the U.S. during the Northern Hemisphere 2015/2016 influenza season to evaluate the immunogenicity and safety of Afluria Quadrivalent in healthy children and adolescents 5 through 17 years old. A U.S.-licensed, quadrivalent inactivated influenza vaccine, Fluarix® Quadrivalent (IIV4), manufactured by GlaxoSmithKline was used as the active comparator. The study was discussed during a 21 April 2015 meeting with Seqirus and agreement was reached with CBER on the final study design. The study was conducted under Seqirus' Afluria Quadrivalent IND 15974. CBER Bioresearch Monitoring (BIMO) issued inspection assignments covering 5 clinical sites. The BIMO inspections did not reveal any issues that would impact the data submitted in this application.

The primary objective of CSLCT-QIV-13-02 was to demonstrate that Afluria Quadrivalent elicits an immune response in children 5 through 17 years of age that is non-inferior to that of the U.S.-licensed IIV4 comparator. The study's co-primary endpoints were geometric mean titer (GMT) ratios and seroconversion rate (SCR) differences calculated from hemagglutination inhibiton (HI) antibody titers for each of the four influenza antigens. Serum antibody titers were measured on Day 1 (pre-vaccination) and 28 days after the last vaccine administration. Seroconversion was defined as either a pre-vaccination HI titer of < 1:10 and a post-vaccination HI titer of ≥ 1:40, or a pre-vaccination HI titer of ≥ 1:10 and a minimum 4-fold rise in post-vaccination HI titer 28 days after the last vaccine administration. To demonstrate non-inferior (NI) immune responses of Afluria Quadrivalent as compared to IIV4, the pre-specified success criteria for the primary endpoints were defined as:

A. The lower bound of the two-sided 95% confidence interval (CI) of the GMT ratio ($GMT_{IIV4}/GMT_{Afluria\ Quadrivalent}$) ≤ 1.5, *AND*

B. The lower bound of the two-sided 95% CI of the SCR difference ($SCR_{IIV4} - SCR_{Afluria\ Quadrivalent}$) ≤ 10%

The above success critia were specified for each of the four vaccine antigens for a total of 8 co-primary study endpoints.

A total of 2278 subjects (Full Analysis Set, FAS) were enrolled and stratified into two cohorts comprised of children 5 through 8 years of age or 9 through 17 years of age. A quota was used to ensure that at least 50% of all subjects were in the 5 through 8 years of age cohort. Demographic and baseline characteristics within each age cohort were similar to the FAS and between treatment groups. Relative to the U.S. population, blacks/African Americans and Hispanics/Latinos were over-represented, and Asians were underrepresented. Following stratification, subjects were randomized 3:1 to receive Afluria Quadrivalent or IIV4 administered intramuscularly. Subjects 9-16 years of age received a single 0.5 mL dose of vaccine. Depending upon their influenza vaccination history, subjects 5-8 years of age received one or two 0.5 mL doses of vaccine 28 days apart as per recommendations by the ACIP.

The Per Protocol Population (PPP, 2133 subjects) was used to analyze the non-inferior immunogenicity primary objective for study CSLCT-QIV-13-02. The PPP was defined as all subjects in the FAS who received vaccine at Visit 1, provided serology specimens with valid serology assay results from both Visit 1 and the Study Exit Visit (Visit 2 or 3), did not experience a laboratory-confirmed influenza illness between Visit 1 and Study Exit Visit, did not receive any prohibited medication during the study that was medically assessed to potentially impact immunogenicity results and who did not have any protocol deviations that were medically assessed as potentially impacting on immunogenicity results. The results for GMTs, GMT ratios, SCRs and SCR differences together with 95% confidence intervals (CIs) are shown in Tables 1 and 2 and demonstrate that the success criteria for study CSLCT-QIV-13-02 were met for each of the 8 co-primary endpoints.

Table 1: Study CSLCT-QIV-13-02 Day 28 Post-Vaccination HI GMTs and GMT Ratios (Per Protocol Population)

Strain	GMT[1] Afluria Quadrivalent (n = 1605)[3]	GMT[1] IIV4 (n = 528)	GMT ratio[2]	GMT Success Criteria Met?
A/H1N1	952.6	958.8	1.01 (0.93, 1.09)[4]	Yes
A/H3N2	886.4	930.6	1.05 (0.96, 1.15)[4]	Yes
B/Yamagata	60.9	54.3	0.89 (0.81, 0.98)[4]	Yes
B/Victoria	145.0	133.4	0.92 (0.83, 1.02)[4]	Yes

Source: Module 5, Section 5.3.5.1 CSLCT-QIV-13-02, Table 11.4-1, Post-Text Table 14.2.1.1.
Abbreviations: A/H1N1=A/California/7/2009 (H1N1) pdm09-like virus; A/H3N2=A/Switzerland/9715293/2013 (H3N2)-like virus; B/Yamagata=B/Phuket/3073/2013-like virus; B/Victoria=B/Brisbane/60/2008-like virus;
[1] GMTs adjusted for covariates: treatment group, age subgroup, sex, vaccination history, pre-vaccination
[2] GMT ratio=GMT_{IIV4} / $GMT_{Afluria\ Quadrivalent}$.
[3] One subject was excluded from the PPP for the adjusted GMT analysis for the GMT ratio because the subject did not have information on all covariates (i.e., unknown previous vaccination history).
[4] Numbers in parentheses are the lower and upper bounds of the 95% confidence interval.

Table 2: Study CSLCT-QIV-13-02 Day 28 Post-vaccination HI seroconversion rates (SCRs) and SCR differences (Per Protocol Population)

Strain	SCR Afluria Quadrivalent (n = 1605)	SCR IIV4 (n = 528)	SCR[1] difference	SCR Success Criteria Met?
A/H1N1	66.4 (64.0, 68.7)[2]	63.3 (59.0, 67.4)	-3.1 (-8.0, 1.8)	Yes
A/H3N2	82.9 (81.0, 84.7)	83.3 (79.9, 86.4)	0.4 (-4.5, 5.3)	Yes
B/Yamagata	58.5 (56.0, 60.9)	55.1 (50.8, 59.4)	-3.4 (-8.3, 1.5)	Yes
B/Victoria	72.1 (69.8, 74.3)	70.1 (66.0, 74.0)	-2.0 (-6.9, 2.9)	Yes

Source: Module 5, Section 5.3.5.1 CSLCT-QIV-13-02, Table 11.4-1, Post-Text Table 14.2.2.1.
Abbreviations: A/H1N1=A/California/7/2009 (H1N1) pdm09-like virus; A/H3N2=A/Switzerland/9715293/2013 (H3N2)-like virus; B/Yamagata=B/Phuket/3073/2013-like virus; B/Victoria=B/Brisbane/60/2008-like virus;
[1] SCR difference=SCR_{IIV4} - $SCR_{Afluria\ Quadrivalent}$.
[2] Numbers in parentheses are the lower and upper bounds of the 95% confidence interval

A secondary objective of study CSLCT-QIV-13-02 was to further characterize the immunogenicity of Afluria Quadrivalent and IIV4 according to age group (5 through 8 years and 9 through 17 years). Except for the B/Yamagata strain in children 5-8 years, Afluria Quadrivalent met immune response criteria recommended by CBER to evaluate seasonal influenza vaccines in subjects 5 through 17 years within each age cohort. These criteria are that, for each of the four vaccine antigens, the lower bound of the 95% CI for

the post-vaccination HI titer of ≥1:40 is at least 70% and that the SCR is at least 40%. Children 5-8 years missed the % HI ≥1:40 endpoint for B/Yamagata by a very small margin in both treatment groups.

Subpopulation Analyses of Immunogenicity

Subanalyses showed a statistically significant trend (non-overlapping 95% CIs) towards higher post-vaccination GMTs for A/H1N1 and A/H3N2 in black as compared to white recipients of Afluria Quadrivalent and non-statistically significant (overlapping 95% CIs) lower SCRs in Hispanic/Latinos as compared to non-Hispanic/Latinos. Immune responses were otherwise similar between sex, race and ethnic groups. The clinical significance of these observations is uncertain and limited by the relatively small sample sizes and descriptive nature of the analyses. The very small sample sizes of other racial groups precluded meaningful analyses.

b) Pediatrics

CBER agreed to the pediatric study plan (PSP) for Afluria Quadrivalent under IND 15974 following review by the FDA Division of Vaccines and Related Products Application and by the FDA Pediatric Review Committee (PeRC). Studies of Afluria Quadrivalent in infants < 6 months of age were waived and studies in children 6 months to 17 years were granted a deferral upon approval of Afluria Quadrivalent in persons 18 years and older (STN 125254/565). The waiver in infants < 6 months of age was granted because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients younger than 6 months of age. The deferral of studies in children 6 months to 17 years was granted because the product was ready for approval for use in adults and the pediatric studies in children 6 months to 17 years of age had not been completed.

The assessment for deferred study CSLCT-QIV-13-02 provided in this supplement was presented to the PeRC on 5 April 2017. The PeRC identified no concerns regarding Seqirus' study assessment.

c) Other Special Populations

Afluria Quadrivalent has not been studied in immunocompromised individuals. Seqirus agreed to establish a prospective pregnancy registry to monitor pregnant women immunized with Afluria Quadrivalent as a postmarketing commitment under STN 125254/565. A separate pregnancy registry was established as a postmarketing commitment for Afluria (trivalent formulation) under STN 125254/259 and has been completed. The study results are pending.

7. SAFETY

The assessment of the safety and tolerability of Afluria Quadrivalent among children 5 through 8 years and 9 through 17 years separately and overall was a secondary objective

of study CSLCT-QIV-13-02. Endpoints used to assess this objective were the frequency and severity of:

A. Solicited local reactions (pain, redness, swelling) and solicited systemic adverse events (AEs) of fever, nausea, vomiting, diarrhea, headache, myalgia, malaise and fatigue through Day 7 after vaccination;

B. Unsolicited AEs for at least 28 days after each vaccination dose;

C. Cellulitis-like reactions (defined as concurrent Grade 3/severe injection site pain, redness, and swelling/lump) for at least 28 days after each vaccination dose.

D. Serious adverse events (SAEs) for 180 days following the last study vaccination dose;

Safety assessments were based on two study populations, the Overall Safety Population (OSP) and the Solicited Safety Population (SSP). The OSP for study CSLCT-QIV-13-02 included 2252 subjects and was defined as all subjects who received a dose of study vaccine and for whom any safety data were available after vaccination. The SSP was used to summarize reactogenicity data and included all randomized subjects who received at least one dose or partial dose of study vaccine and provided any evaluable data on solicited events (2156 subjects).

Solicited local reactions and solicited systemic AEs

The SSP was used to assess solicited local reactions and solicited systemic AEs. Of the 2156 SSP subjects, 1621 received Afluria Quadrivalent and 535 received IIV4. Rates for any and individual solicited local reactions following any vaccination stratified according to age are shown in Table 3.

Table 3: Study CSLCT-QIV-13-02 rates of solicited local reactions following any vaccination

Solicited local reaction	Afluria Quadrivalent 5-8 years (n = 829)	IIV4 5-8 years (n = 274)	Afluria Quadrivalent 9-17 years (n = 792)	IIV4 9-17 years (n = 261)
Any	57.2%	54.0%	54.9%	50.2%
Pain	51.3%	49.6%	51.5%	45.2%
Redness	19.4%	18.6%	14.8%	16.1%
Swelling	15.3%	12.4%	12.2%	10.7%

Among subjects 5 through 8 years who received two vaccinations (Afluria Quadrivalent n=178, IIV4 n=63), rates of all local reactions and severe reactions were lower following the second dose. For subjects 9-17 years, most reactions were mild in severity and the overall rates of any severe local reaction were similar between treatment groups (Afluria Quadrivalent = 3.2%, IIV4 = 3.8%).

The rates of solicited systemic AEs following any vaccination stratified according to age are shown in Table 4.

Table 4: Study CSLCT-QIV-13-02 rates of solicited systemic adverse events following any vaccination

Solicited systemic AE	Afluria Quadrivalent 5-8 years (n = 829)	IIV4 5-8 years (n = 274)	Afluria Quadrivalent 9-17 years (n = 792)	IIV4 9-17 years (n = 261)
Any	27.6%	26.3%	34.1%	28.7%
Headache	12.3%	10.6%	18.8%	14.6%
Myalgia	9.8%	11.3%	16.7%	11.1%
Malaise/fatigue	8.8%	5.8%	10.0%	7.7%
Nausea	7.1%	8.4%	7.7%	8.0%
Diarrhea	5.2%	3.6%	5.4%	4.2%
Vomiting	2.4%	4.4%	1.8%	2.3%
Any Fever (≥100.4°F)	4.5%	3.6%	2.1%	0.8%
Severe Fever (≥102.2°F)	1.2%	0.7%	0.5%	0.0%

Among subjects 5-8 years old, most events were mild to moderate in severity with a total of 1.6% and 1.5% of Afluria Quadrivalent and IIV4 recipients, respectively, reporting severe systemic AEs (predominantly fever). Rates of solicited systemic AEs following the second vaccination were lower than the first vaccination among subjects 5-8 years in both treatment groups who received two vaccinations. Fever occurred in 4.0% and 3.0% of Afluria Quadrivalent and IIV4 recipients, respectively, after the first vaccination and in 2.2% and 3.2%, respectively, after the second vaccination. No fevers were associated with seizures. No subjects in either treatment group reported severe solicited systemic AEs, including fever ≥102.2°F, following the second vaccination.

Severe solicited systemic AEs were uncommon among subjects 9-17 years old, occurring in 1.4% and 0.8% of Afluria Quadrivalent and IIV4 recipients, respectively. No fevers occurring in subjects 9-17 years old were associated with seizures.

Unsolicited AEs

A total of 310 subjects (13.8%) 5 through 17 years from the OSP reported 503 unsolicited AEs in the 28 days following vaccination(s). A slightly higher proportion of Afluria Quadrivalent recipients (14.4%) reported unsolicited AEs as compared to IIV4 (12.0%), and higher overall rates of AEs among subjects 5-8 years (Afluria Quadrivalent 16.2%; IIV4 15.0%) as compared to subjects 9-17 years (Afluria Quadrivalent 12.5%; IIV4 8.8%) in both treatment groups were reported. Among recipients of Afluria Quadrivalent 5 through 8 years, the most common (frequency ≥1%) unsolicited AEs were: cough (2.4%), pyrexia (1.8%), rhinorrhea (1.2%), and headache (1.0%). Among recipients of Afluria Quadrivalent 9 through 17 years, the most common unsolicited AEs were: oropharyngeal pain (1.6%), cough (1.3%), and upper respiratory tract infection (1.0%). Most events were mild to moderate in severity and appeared unrelated to study vaccine. Overall, no clinically significant vaccine-related large imbalances or unusual patterns were observed between age and treatment groups.

Cellulitis-like reactions

One 8-year old recipient of Afluria Quadrivalent had a non-serious cellulitis-like reaction with accompanying moderately severe systemic AEs following the first vaccination. All events resolved with treatment within 11 days of vaccination. This case of cellulitis will be included in Section 6.1, *Clinical Trials Experience*, of the Afluria Quadrivalent package insert. No IIV4 recipients reported cellulitis-like reactions during the 28 days following last vaccine administration.

SAEs

The OSP was used for the assessment of SAEs and included 1692 Afluria Quadrivalent and 560 IIV4 recipients. Eight Afluria Quadrivalent and two IIV4 recipients within the OSP reported a total of 13 SAEs. Six of the eight Afluria Quadrivalent and both IIV4 recipients reporting SAEs were in the 9-17 year old cohort. Most (11) SAEs occurred >28 days post-vaccination and were not unusual diagnoses in a pediatric and adolescent population. With the exception of a case of influenza B infection that may be considered a vaccine failure and in that context related, none of the SAEs appeared related to study vaccines based on a lack of close temporal relationship, lack of biological plausibility, and/or the presence of a more likely pathophysiological mechanism. No deaths occurred during the 6 month safety follow-up period. No subjects discontinued the study due to AEs.

Subpopulation Analyses of Safety

Rates of deaths and SAEs in CSLCT-QIV-13-02 were too low to perform meaningful subpopulation analyses.

Sub-population analyses of solicited AEs among Afluria Quadrivalent recipients showed a trend toward slightly higher rates of injection site pain and swelling and headache in females as compared to males, and higher rates of fever in males relative to females. Blacks/African Americans reported less local and systemic reactogenicity as compared to whites following vaccination with Afluria Quadrivalent and, overall, Hispanic/Latinos reported less solicited local reactions and systemic symptoms than non-Hispanic/Latinos following vaccination with Afluria Quadrivalent.

Overall rates of unsolicited AEs in Afluria Quadrivalent recipients 5-17 years were similar between males and females (14.8% and 13.9%, respectively). Sub-population analyses revealed a trend towards lower overall rates of unsolicited AEs in black/African American recipients of Afluria Quadrivalent as compared to whites (11.7% vs 15.3%, respectively) and in Hispanic/Latino recipients of Afluria Quadrivalent as compared to non-Hispanic/Latinos (10.6% vs 15.6%). Small sample sizes precluded meaningful sub-analyses of other racial groups. Because the study was not designed to detect statistically significant differences between subpopulations, firm conclusions cannot be drawn from the observed trends.

8. ADVISORY COMMITTEE MEETING

No issues were identified during the review of the supplement that would necessitate presentation before an advisory committee.

9. OTHER RELEVANT REGULATORY ISSUES

No other relevant regulatory issues were identified during the review of this supplement.

10. LABELING

The Afluria Quadrivalent package insert was revised to include safety and immunogenicity data for children 5-17 years of age from study CSLCT-QIV-13-02. The review committee negotiated revisions to Sections 8.1, *Pregnancy*, and 8.2, *Lactation*, of the package insert (PI) to be consistent with the 2014 draft FDA Guidance for Industry, "*Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products - Content and Format*".

The Advertising and Promotional Labeling Branch (APLB) found the prescribing information and carton/container labels for Afluria Quadrivalent to be acceptable from a promotional and comprehension perspective.

11. RECOMMENDATTIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

The Review Committee recommends approval of Afluria Quadrivalent in children 5-17 years based on the data demonstrating that Afluria Quadrivalent elicited a non inferior immune response in this population as compared to IIV4 and based upon the vaccine's acceptable safety profile.

b) Risk/ Benefit Assessment

Afluria Quadrivalent demonstrated non-inferior immunogenicity to a U.S.-licensed comparator IIV4 in a pediatric population 5 through 17 years, suggesting that it is likely to confer protection against influenza similar to Afluria (trivalent formulation) for strains common to both vaccines, and additional protection against the alternate B strain as compared to the trivalent formulation. Lower immune responses elicited against the influenza B vaccine antigens as compared to influenza A were observed for both Afluria Quadrivalent and the comparator, and have also been observed in studies of other IIVs. Because Afluria Quadrivalent is manufactured by the same process as Afluria (trivalent formulation) and has demonstrated non-inferior immunogenicity, a clinical endpoint study to confirm clinical benefit is not necessary.

The safety profile of Afluria Quadrivalent was comparable to a U.S.-licensed IIV4 and was clinically acceptable. Small imbalances in solicited AEs, including fever, suggest that Afluria Quadrivalent was slightly more reactogenic than the comparator, however, the differences did not appear clinically significant because overall rates were low and no events were serious. Notably, rates of fever among subjects 5-8 years, in the 7 days following vaccination with Afluria Quadrivalent were lower than historical rates for Afluria (trivalent formulation). Consistent with conclusions from Seqirus' scientific investigation of the root cause of febrile seizures and other febrile events associated with the SH 2010 formulation of Afluria, (b) (4) the four Afluria Quadrivalent vaccine virus strains used in study CSLCT-QIV-13-02 appears associated with less pyrogenicity. Given the effectiveness against a potentially serious and life-threatening disease, it is reasonable to conclude that the potential benefits of Afluria outweigh potential risks in children and adolescents 5 through 17 years. Routine postmarketing surveillance appears sufficient and will help clarify whether the lower rates of fever observed in CSLCT-QIV-13-02 are generalizable to a broader population 5-17 years or to future vaccine formulations containing different antigens.

c) Recommendation for Postmarketing Activities

No new postmarketing activities were deemed necessary. A PREA-required postmarketing study of Afluria Quadrivalent in infants/children 6 months through 4 years of age and a postmarketing commitment to initiate a pregnancy registry for Afluria Quadrivalent recipients were established under STN 125285/565.