Summary Basis for Regulatory Action

Date: August 24, 2016

From: Richard Daemer**,** Chair of the Review Committee

BLA/ STN#: 125254/565

Applicant Name: Seqirus Pty Ltd (formerly bioCSL, Pty, Ltd)

Date of Submission: October 28, 2015

PDUFA Goal Date: August 27, 2016

Proprietary Name/ Established Name: Afluria Quadrivalent, Quadrivalent Influenza Vaccine

Indication: Active immunization against influenza disease caused by Influenza A subtype viruses and type B viruses contained in the vaccine for adults ≥18 years.

Recommended Action: Approval

Signatory Authorities Action: Approval

Offices Signatory Authority: Wellington Sun, M.D., Director, Division of Vaccines and Related Products Applications, office of Vaccine 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.**

Material Reviewed/ Consulted	**Specific documentation used in developing the SBRA Reviewer Name – Document(s) Date -**
Clinical Review	Cynthia Nolletti, MD - August 16, 2016
Regulatory	CAPT Katherine Berkhousen, RN
Regulatory	Timothy Fritz, PhD
Statistical Review	Rong Fu, PhD - July 20. 2016
CMC/ Review	Falko Schmeisser, PhD – July 20, 2016
Bioresearch Monitoring Review	Anthony Hawkins, MS – March 31, 2016
Pharmacovigilance Review	Wambui Chege, MD – June 14, 2016
Quality Control Review	Marie Anderson, PhD – May 27, 2016
Quality Control Review	Manju Joshi, PhD – July 7, 2016

Quality Control Review	Tao Pan, PhD – July 19, 2016
Quality Control Review	Claire Wernly, PhD – May 24, 2016
Facilities Review	LCDR Donald Ertel, MS, MT – May 2, 2016
Facilities Review	Nicole Li, MS – May 2, 2016
Bioresearch Monitoring Review	Anthony Hawkins, MS – Mar 31, 2016
Labeling Review	Sonny Saini – July 14, 2016
Carton/Container Review	Daphne Stewart – August 16, 2016
Electronic Integrity Review	LCDR David Schwab. MS

1. Introduction

Afluria is an influenza vaccine indicated for active immunization against influenza caused by the influenza virus subtypes A and B present in the vaccine. Afluria is produced by Seqirus Pty (formerly CSL Behring) and was first approved by the Food and Drug Administration (FDA) on September 28, 2007. The product is approved for use in persons 5 years of age and older and is supplied in two presentations – as a 0.5 mL pre-filled single dose syringe or as a 5 mL multi-dose vial which contains ten 0.5 mL single doses.

The current formulation of Afluria is a trivalent inactivated influenza vaccine (TIV) containing 45 mcg hemagglutinin (HA) per 0.5 mL dose in the recommended ratio of 15 mcg HA for each of the three influenza strains recommended for the 2015-2016 Northern Hemisphere influenza season: A/California/7/2009 (H1N1), NYMC X-181; A/South Australia/55/2014 (H3N2), IVR-175 and B/Phuket/3073/2013. CSL markets its trivalent inactivated influenza vaccine under the brand name Afluria in the US, as Fluvax in the Southern Hemisphere (SH) and as Enzira in the United Kingdom.

Each single 0.5 mL dose of Afluria TIV contains sodium chloride (4.1 mg), monobasic sodium
(80 mcg), dibasic sodium phosphate (300 mcg), monobasic potassium phosphate (20 mcg), p chloride (20 mcg), and calcium chloride (1.5 mcg). From the manufacturing process, each 0.5 may also contain residual amounts of sodium taurodeoxycholate (≤ 10 ppm), ovalbumin (≤ 1 sucrose (<10 mcg), neomycin sulfate (≤ 3 nanograms [ng]), polymyxin B (≤ 0.5 ng), and beta propiolactone (≤ 2 ng). The multi-dose presentation of Afluria TIV also contains thimerosal a preservative, such that each 0.5 mL dose in a multi-dose vial contains 24.5 mcg of mercury.

In this efficacy supplement, submitted on October 28, 2015 the sponsor has submitted safety and immunogenicity data to support an indication for a new quadrivalent formulation (QIV) containing two type B virus strains, representing both B virus genetic lineages (Yamagata and Victoria), for use in adults ≥18 years of age.

2. Background

Influenza is an important infectious cause of death in the U.S. and throughout the world, with influenza-associated respiratory and circulatory mortality rates ranging from 3,349 to 48,614 in the U.S. from 1976 to 2007 (average annual mortality of 23,607) and 250,000 to 500,000 deaths worldwide each year. It is responsible for more deaths in the U.S. than all other vaccine-preventable diseases combined. In seasons when influenza A/H3N2 predominates, mortality has been 2.7 times higher than when other strains (A/H1N1 or B) have predominated. A Centers for Disease Control and Prevention (CDC) study covering the period 1990-1999, during which A/H3N2 predominated in the U.S., estimated an annual average mortality of 36,155. During seasonal influenza epidemics in the U.S. from 1979-2001, the CDC estimated that influenza-associated hospitalizations ranged from 55,000 to 431,000 per season. Complications, hospitalizations and deaths from seasonal influenza disproportionately affect persons $\geq$ 65 years, children < 5 years (especially those < 2 years), and persons of any age with certain underlying cardiac, respiratory, metabolic, or immune compromising medical conditions

Influenza is caused by RNA viruses of the family Orthomyxoviridae. Two types, influenza A and B, cause the vast majority of human disease. Influenza A is further categorized into subtypes based on two principal surface antigens, hemagglutinin (HA) and neuraminidase (NA), which comprise the viral glycoprotein coat. There are multiple subtypes of Influenza A based on combinations of 18 variants of HA and 11 variants of NA, but only subtypes H1N1, H2N2, and H3N2 appear to circulate in humans. Influenza A has also been isolated from non-human species including birds, horses, and swine. In contrast to influenza A, influenza B is comprised of single HA and NA subtypes, and is only known to occur in humans. Antibodies to influenza surface antigens are subtype and strain-specific, and confer protection against future infection with identical strains, but not against another type or subtype. Historically, the A/H3N2 strain has been associated with a higher mortality rate as compared to the A/H1N1 or B strains, although the B strain is known to cause serious disease in children.

Since 1977, influenza A subtypes H1N1 and H3N2 and influenza B have co-circulated globally. Seasonal epidemics generally occur during the winter months and are caused by antigenic drift, new antigenic variants or viral strains that result from point mutations in the viral genome that occur during replication. Antigenic variants or strain changes occur each year necessitating annual change in the formulation of influenza vaccines for optimal protection. Neutralizing antibody against HA is the primary immune defense against infection with influenza. Although there is no established absolute immune correlate of protection, studies have suggested that HI titers of 1:32 to 1:40 correlate with protection against illness. This strain-specific immune response appears to predict a clinical endpoint of efficacy with reasonable certainty. Previous experience with inactivated influenza vaccines supports use of HI titers as a surrogate endpoint.

3. Chemistry Manufacturing and Controls (CMC)

The antigen manufacture, vaccine formulation and fill and finish processes for Afluria QIV are consistent with those approved for Seqirus Trivalent Influenza Vaccine (TIV, Afluria; STN 125254), with the exception of the addition of a second influenza B strain to the formulation, which will increase the Hemagglutinin (HA) content from 45 to 60 µg HA per 0.5 mL dose.

The Drug Substance, for Afluria QIV is the same as that used for TIV - a sterile, aqueous suspension of an individual, inactivated, influenza virus strain (type A or B) that had been grown in fertilized chicken eggs, inactivated and disrupted, resulting in a split virion, inactivated Monovalent Pooled Harvest (MPH).

a) Product Quality

The Drug Substance manufacturing process and process controls for Seqirus' Afluria QIV are aligned with those licensed for Afluria TIV. The Monovalent Pooled Harvest is produced at Seqirus' FDA-licensed dedicated Influenza Virus Vaccine production facility in Parkville (Victoria, Australia), by inoculating influenza virus into the allantoic cavity of embryonated chicken eggs, and then incubating the eggs for approximately [redacted]. The virus-rich allantoic fluid is harvested, purified, inactivated by Beta-Propiolactone (BPL), split by detergent Sodium taurodeoxycholate (TDOC), [redacted]

The starting material for each Monovalent Pooled Harvest is the influenza virus seed lot. The Master Virus Seed lot and Working Virus Seed lot are prepared from a candidate vaccine virus received from a World Health Organization (WHO) approved custodian laboratory, and are manufactured in accordance with the process and controls as detailed in the Afluria TIV BLA 125254. In the QIV sBLA, the applicant submitted details of Working Virus Seed lots used for each QIV lot produced to date. The raw materials and solutions used in the manufacture of Monovalent Pooled Harvest for QIV are identical with those approved for TIV.

The following strains are included in Afluria for the 2016-2017 US influenza season:

Virus Strain	***Working Virus Seedlot***
A/California/7/2009 NYMC X-181 (H1N1)	(b) (4)
A/Hong Kong/4801/2014 NYMC X-2638 (H3N2)	(b) (4)
B/Brisbane/60/2008 (B, Victoria lineage)	(b) (4)
B/Phuket/3073/2013 (B, Yamagata lineage)	(b) (4)

The seed viruses of all four strains are in accordance with recommendations by FDA and WHO for the 2016-2017 flu season in the northern hemisphere. The sBLA submission contains documentation on how the seed viruses were derived, their

passage histories, and CBER certifications that confirm antigenic identity. All seed viruses have been tested for antigenic identity, certified, and approved for use by CBER. Therefore, these seed viruses have been determined to be suitable for the 2016-2017 vaccine preparation.

To support the manufacture of the QIV drug product, Seqirus submitted a process validation. The drug product manufacturing process for QIV and TIV is nearly identical except during formulation. Specifically, the addition of an extra influenza type B strain occurs during the step "Addition of MPH to Formulation Vessel" to produce QIV. When a combination of the four influenza strains (MPHs) and thimerosal preservation (required only for TC QIV) are suspended in a phosphate buffered solution (Vaccine Diluent), the product is referred to as the Final Bulk Vaccine (FBV). All steps downstream from the FBV are the same for the QIV and TIV drug product.

b) CBER Lot Release

A review of Product Release Branch records indicate that there are no pending lots or issues that would affect approval of the submission. Revisions to the Lot Release Protocol Template submitted by Seqirus were found to be acceptable.

c) Facilities Review and Inspection

Facility information and data provided in the Efficacy Supplement were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of Afluria QIV TF (Thimerosal-free) and Afluria QIV TC (Thimerosal-containing) are listed in the table below. The activities performed and inspectional histories are noted in the table and are further described in the paragraphs that follow.

Manufacturing Facilities Table for Afluria QIV (Quadrivalent Influenza Vaccine)

Name/Address	FEI Number	DUNS Number	Inspection / Waiver	Justification / Results
Drug Substance Seqirus Pty Ltd (formerly bioCSL, Pty, Ltd) 63 Poplar Road Parkville, Victoria, Australia, 3052	3002806753	747286735	Waived	Team Biologics June 5 – 13, 2014 VAI
Drug Product (QIV TF and QIV TC): *Formulation, Fill/Finish, Labeling & Packaging, Release Testing* CSL Behring GmbH	3003098680	326530474	Waived	DMPQ/CBER May 28 – June 5, 2015 VAI

Emil-von-Behring Strasse 76 Marburg, Hesse, Germany, 35041				
Drug Product (QIV TF): Formulation, Fill/Finish, Labeling & Packaging, Release Testing CSL Behring LLC (b) (4)	(b) (4)	(b) (4)	Waived	ORA (b) (4) NAI

Team Biologics conducted a surveillance inspection of Seqirus Pty Ltd (formerly bioCSL, Pty, Ltd) from June 5 – 13, 2014. All 483 issues were resolved and the inspection was classified as voluntary action indicated (VAI).

DMPQ/CBER conducted a Pre-License Inspection (PLI) of CSL Behring GmbH from May 28 – June 5, 2015 for Coagulation Factor IX (Recombinant), Albumin Fusion Protein (rIX-FP), STN 125582/0. Upon completion of the PLI, a Form FDA 483 with 19 observations was issued. The firm addressed the 19 observations with a written response to the FDA, which was determined to be adequate. The inspection was classified as voluntary action indicated (VAI).

ORA conducted a surveillance inspection of (b) (4) . No Form FDA 483 was issued and the inspection was classified as no action indicated (NAI).

d) Environmental Assessment

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

e) Container Closure

The container closure system for QIV TF (Thimerosal-free) Drug Product is identical to that used for TIV TF. Accordingly, QIV TF is dispensed into a 1.25 mL clear (b) (4) glass needle-free syringe and sealed with a chlorobutyl stopper/polystyrene plunger rod assembly. The (b) (4) glass syringe barrel has a Luer-Lok® adapter to permit the attachment of a commercially available needle prior to administration. The Luer-Lok® adapter is sealed with a bromobutyl/isoprene rubber tip cap with a polypropylene shield for protection

against damage and contamination. All container closure components are manufactured by (b) (4) .

The container closure system for QIV TC (Thimerosal-containing) Drug Product is the same that is used for TIV TF. QIV TC is presented in 5.0 mL (b) (4) , clear, (b) (4) glass multi-dose vials (b) (4) . The glass vial is closed with a bromobutyl or chlorobutyl rubber stopper ((b) (4) The stopper is secured by combination caps (b) (4) which consist of an aluminum cap with a concentric hole and an integrated polypropylene plastic disc.

As the container closure systems are the same as those licensed for TIV, no container closure integrity testing was performed for QIV TF and QIV TC. Container closure integrity had been previously validated by (b) (4) testing and (b) (4) testing with all acceptance criteria met.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical or toxicology studies were performed in support of the current supplement.

5. Clinical Pharmacology

No clinical pharmacology data were requested or submitted in the context of this submission.

6. Clinical/ Statistical

a) Clinical Program

Data was submitted from a single study, CSLCT-QIV-13-01, to support the safety and effectiveness of Afluria QIV in adults 18 years and older. CSLCT-QIV-13-01 was a prospective, phase 3, observer-blind, comparator-controlled, multicenter study conducted in the U.S. during the Northern Hemisphere (NH) 2014-2015 influenza season in 3484 healthy adults ≥18 years, stratified by age (18 through 64 years and ≥65 years), and randomized 2:1:1 to receive Afluria QIV, U.S.-licensed 2014-2015 Afluria TIV-1 (Afluria), or Afluria TIV-2 containing the alternate B virus strain.

The primary objective of the study was to demonstrate that vaccination with Afluria QIV elicits an immune response that is not inferior to that of Afluria TIV containing the same virus strains as the U.S.-licensed 2014-2015 Seqirus influenza vaccine trivalent formulation (Afluria TIV-1), and the TIV containing the alternate B strain (Afluria TIV-2) among adults aged ≥18 years. The study was powered to demonstrate the non-inferior immunogenicity of Afluria QIV as compared to Afluria TIV-1 and TIV-2 in two age strata, adults 18 through 64 years and ≥65 years, as a secondary objective. Other secondary objectives were to demonstrate the immunological

superiority of Afluria QIV compared to Afluria TIV-1 and TIV-2 for the B strain that was not included in each TIV vaccine separately, and to assess the reactogenicity and safety of Afluria QIV.

Summary of Immunogenicity

The Per Protocol Population (PPP) was used for the primary and secondary immunogenicity analyses and included a total of 3395 subjects, 1691 of whom received Afluria QIV, 854 Afluria TIV-1, and 850 Afluria TIV-2. Afluria QIV elicited immune responses that met all eight pre-specified co-primary endpoints of GMT ratios and SCR differences for the four vaccine antigens required to demonstrate NI to the Afluria comparator TIV vaccines in adults ≥18 years of age. For all four antigens, the upper bound (UB) of the two-sided 95% confidence interval (CI) GMT ratio for Afluria TIV-1 and 2 / Afluria QIV did not exceed 1.5. Four all four antigens, the UB of the two-sided 95% CI for the SCR difference for Afluria TIV-1 and 2 – Afluria QIV did not exceed 10%. Afluria QIV also met all co-secondary endpoints of GMT ratios and SCR differences for each antigen within each age stratum of subjects 18-64 years and ≥65 years, demonstrating NI to the TIV comparators in each age group. Afluria QIV met secondary HI GMT and SCR endpoints and pre-specified criteria for superior GMT ratios and SCR differences for each B strain as compared to U.S.-licensed Afluria TIV-1 and TIV-2 containing the alternate B strain, demonstrating immunological superiority against the alternate B strains within both age cohorts 18-64 years and ≥65 years and overall. Secondary immunogenicity endpoints of post-vaccination GMTs, proportions of with post-vaccination HI titers ≥1:40, and SCRs showed that immune responses were similar between Afluria QIV and the two TIV comparators, overall and within each age cohort. However, as has been observed in other influenza vaccine studies, SCRs to all vaccine virus strains were significantly lower in adults ≥65 years of age as compared to the younger age cohort.

b) Pediatrics

Afluria QIV triggered the Pediatric Research Equity Act (PREA) because it contains a new active ingredient (a second influenza type B virus antigen). Accordingly, the submission included a Pediatric Study Plan (PSP) and requests for a partial waiver and deferral of pediatric studies. Studies in children from birth to < 6 months of age will be waived because Afluria QIV does not represent meaningful therapeutic benefit over initiating vaccination at 6 months of age and is not likely to be used in a substantial number of infants younger than 6 months. Assessments in two pediatric age groups (children and adolescents aged 5 through 17 years, and children aged 6 months through 4 years) are deferred because the product is ready for approval for use in adults, and pediatric studies have not been completed. The Pediatric Research Committee (PeRC) agreed with the Applicant's PSP on February 10, 2016.

c) Other Special Populations

There were no other populations studied.

d) Overall Comparability Assessment

Overall, Afluria QIV demonstrated non-inferior immunogenicity as compared to Afluria TIV-1 and Afluria TIV-2 containing the alternate B strain in adults 18 years and older.

e) BIMO Inspection

Bioresearch Monitoring inspections of four U.S. clinical investigator study sites were conducted in support of this Biologics Licensing Application (BLA) prior approval supplement. The sites were selected based upon numbers of enrolled study subjects, prior FDA inspection history and numbers and types of adverse events and protocol deviations. The inspections were conducted in accordance with FDA's Compliance Program Guidance Manual (CPGM) 7348.811, Inspection Program for Clinical Investigators. Results from the inspections did not reveal substantive problems that impact the data submitted in the BLA.

7. Safety

Overall, a total of 37.4% of subjects experienced solicited local adverse reactions after vaccination with Afluria QIV as compared to similar rates following TIV-1 (34.6%) or TIV-2 (36.6%). More adults 18-64 years of age reported solicited local adverse reactions as compared to adults ≥65 years of age (48.4% vs 26.6%). In both age cohorts pain was the most common injection site reaction (47.9% of adults 18-64 years and 24.6% of adults ≥65 years). Slightly higher proportions of Afluria QIV recipients reported measured injection site erythema (4.2% vs 2.1%-2.5%) and induration (3.2% vs 1.6%-1.8%) as compared to recipients of TIV-1 and TIV-2, but rates were low overall. Most local reactions were mild to moderate in severity, with <1% reported as severe across age and treatment groups. The majority of local reactions resolved within two to three days.

A total of 28.9% of subjects experienced solicited systemic AEs after vaccination with Afluria QIV as compared to similar rates following TIV-1 (28.4%) or TIV-2 (27.2%). More adults 18-64 years of age reported solicited systemic adverse events following Afluria QIV as compared to adults ≥65 years of age (38.3% vs 19.7%). The most common events across both age cohorts (>10%) were muscle ache/myalgia and headache. Fever was uncommon, 0.5%-0.9% across treatment and age groups. Most solicited systemic events were mild to moderate in severity, with 2.0% of all subjects experiencing severe symptoms. No large imbalances were noted across treatment groups. The majority of systemic symptoms resolved within one to two days. No large imbalances were noted across treatment groups.

Due to concerns for a potential increase in local reactogenicity with the addition of a second B strain antigen relative to the trivalent formulation, which had increased reports of local cellulitis reactions during the 2011-2012 Northern Hemisphere season,

monitoring of severe (Grade 3) induration/swelling, cellulitis-like reactions, and cellulitis at the injection site were pre-specified safety endpoints in CSLCT-QIV-13-01. Although the total number of subjects who experienced Grade 3 injection site induration/swelling in the study was relatively low (n=6/3449, 0.17%), there was a clear imbalance between severe injection site swelling in subjects treated with Afluria QIV (0.3%) as compared to recipients of Afluria TIV-1 or TIV-2 (0.06%). Whether this was due to chance alone or to greater reactogenicity caused by an additional B strain antigen is not known. Postmarketing surveillance for such reactions will continue following approval of Afluria QIV.

A total of 89 SAEs (including deaths) were experienced by 66 subjects during the six month safety follow-up period. Of these, 15 SAEs occurred in 12 subjects within the 28 days post-vaccination. Overall, more recipients of Afluria QIV reported SAEs as compared to recipients of TIV-1 or TIV-2 (2.3% versus 1.6%, and 1.5%, respectively), and more subjects in the older age cohort ≥65 years experienced SAEs as compared to younger adults 18-64 years of age (3.0% versus 0.8%). No specific SAE or group of events categorized either by MedDRA PT or SOC occurred with a frequency of ≥1%, and no specific imbalance or pattern was observed across treatment groups. The majority of SAEs appeared unrelated to the study vaccines due to a lack of a strong temporal relationship, lack of biological plausibility, and/or an alternative causal explanation.

A total of 719 subjects (20.8%) reported 1343 spontaneous or unsolicited AEs in the 28 days following vaccination, with similar proportions across treatment groups and age cohorts. Frequencies of individual events were low and similar across treatment groups and between age cohorts. The most common unsolicited AEs overall were headache (3.5%), oropharyngeal pain (1.8%), and back pain (1.7%). No large imbalances or unusual patterns were observed. Most events were mild to moderate in severity and appeared unrelated to study vaccine.

Overall, 2.8% of subjects discontinued the study, most were lost to follow-up (2.4%), and none were due to AEs. The dropout/discontinuation rates were low, similar across treatment groups, and should not have introduced significant bias or influenced the interpretation of safety results.

8. Advisory Committee Meeting

A Vaccines and Related Biological Products Advisory Committee Meeting for the discussion of the data in this submission was not held because review of this supplement did not raise concerns which would have benefited from an advisory committee discussion.

9. Other Relevant Regulatory Issues.

Given the available safety data, the PVP proposed for Afluria QIV by the sponsor appears adequate for monitoring known safety concerns and collecting missing information. The proposed pregnancy study may be listed on the approval letter as a postmarketing commitment study (PMC). At this time, the available safety information does not necessitate a required postmarketing safety study (PMR), or Risk Evaluation and Mitigation Strategies (REMS).

Seqirus commits to providing an updated Risk Management Plan for Afluria QIV that includes large/extensive injection site swelling and cellulitis-like reactions as important potential risks by September 2016.

10. Labeling

The reviewer from Advertising and Promotional labeling Branch (APLB) and other committee members evaluated the package insert (PI). After revisions to the wording of the PI, which were agreed to in discussions with the applicant, the review committee determined that the prescribing information as it pertains to the use of Afluria QIV in adults 18 years and older is acceptable.

Major changes to the Applicant's draft new PI and areas of negotiation were:

- Highlights, Dosage and Administration [2], and Warnings and Precautions [5]: Removed dosage table; removed warning that safety and effectiveness have not been established in persons <18 years; removed warning that immune responses may be diminished in immunocompromised persons; removed statement that safety and effectiveness have not been established in pregnant women or nursing mothers.
- Adverse Reactions [6.1]: Added description of monitoring for severe injection site reactions and cellulitis.
- Postmarketing Experience [6.2]: Modified to be consistent with the Afluria (trivalent) labeling supplement (STN 125254.563).
- Pregnancy [8.1] and Lactation [8.2]: Modified to conform to the new PLLR.

The package and container labeling were found to be acceptable.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The committee recommends approval of the BLA supplement.

b) Risk/ Benefit Assessment

The overall risk/benefit of the product is favorable based on the data submitted in the submission. Afluria TIV has demonstrated clinical efficacy in adults 18-49 years (STN

125254.259). Afluria QIV demonstrated non-inferior immunogenicity in comparison to trivalent formulations of Afluria in both adults and elderly adults, suggesting that it is likely to confer protection similar to Afluria TIV for the strains common to both vaccines, and additional protection against the alternate B strain as compared to the trivalent formulation. The lower immune responses elicited in elderly subjects relative to adults 18-64 years, particularly against the influenza B vaccine antigens have also been observed in studies of other IIVs. Because Afluria QIV is manufactured by the same process as Afluria TIV and has demonstrated non-inferior immunogenicity, a clinical endpoint study to confirm clinical benefit is not necessary.

The safety data supporting licensure suggest slightly higher rates of severe local reactogenicity for Afluria QIV as compared to the trivalent formulations but the rates were very low and the events were non-serious and self-limited. Routine postmarketing surveillance for severe injection site reactions appears sufficient at this time. As clinical trials of Afluria QIV proceed in children <9 years, CBER recommends closer monitoring for febrile reactions and stringent halting rules.

c) Recommendation for Postmarketing Risk Management Activities

At this time, OBE /DE does not recommend a REMS or a PMR designed specifically to evaluate a particular safety concern as a primary endpoint for Afluria QIV.

d) Recommendation for Postmarketing Activities

Two phase 3 pediatric postmarketing requirements (PMRs) are required:

1. A deferred pediatric study under required under PREA, to evaluate the immunogenicity and safety of Afluria Quadrivalent in the pediatric population 5 through 17 years of age.

2. A 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 sponsor agreed to the following post-marketing commitment:

> 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.