Summary Basis for Regulatory Action

Date: December 1, 2011

From: Timothy Fritz, Ph.D., Review Committee Chair

BLA/ STN: 125254/259

Applicant Name: CSL Limited

Date of Submission: November 23, 2010

PDUFA Goal Date: December 2, 2011

Proprietary Name/Established Name: Influenza Virus Vaccine/AFLURIA®

Indication: AFLURIA is indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. AFLURIA is approved for use in persons 5 years of age and older.

Recommended Action: Approval

Signatory Authorities Action: Approval

Offices Signatory Authority: Wellington Sun, M.D., Director, DVRPA
☐ **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.**

Specific Documentation used in Developing the SBRA	**Reviewer**
Clinical Review	Cynthia Nolletti, M.D.
Pharmacovigilance Review	Michael Nguyen, M.D.
Statistical Review, Clinical	Tammy Massie, Ph.D.
Statistical Review, Bioassay	Lihan Yan, Ph.D.
Biomonitoring Review	Lillian Ortega
Product Review	Falko Schmeisser, Ph.D. Galina Vodeiko, Ph.D.
Labeling Reviews	Cynthia Nolletti, M.D. Tammy Massie, Ph.D. Maryann Gallagher Timothy Fritz, Ph.D.
Communications and Documentation	Timothy Fritz, Ph.D. Goutam Sen, Ph.D.

1. INTRODUCTION

AFLURIA was approved for active immunization against influenza in adults 18 years of age and older on September 28, 2007 under accelerated approval regulations. Approval was extended to children 6 months to < 18 years of age on November 10, 2009. Due to safety concerns regarding pediatric febrile seizures observed after CSL's Southern Hemisphere influenza vaccine fromulation, Fluvax,, FDA revised the use of AFLURIA from persons ≥ 6 months of age to persons ≥ 5 years of age on July 15, 2011 in the approval of CSL's 2011/2012 influenza strain change supplement STN 125254/303.

AFLURIA is a suspension for intramuscular injection. Each 0.5 mL dose of AFLURIA is formulated to contain 15 µg hemagglutinin (HA) from each of three influenza viruses from subtypes H1N1 and H3N2 and type B. AFLURIA is supplied in preservative-free, single dose, pre-filled syringes and multidose vials. Multidose vials contain 0.01% thimerosal per dose (24.5 µg of mercury) as a preservative.

This supplement (STN 125254/259) was submitted on November 23, 2010, to gain traditional approval for AFLURIA and included the results from the following 4 clinical studies:

a. Study CSLCT-USF-06-28 (a clinical endpoint efficacy, safety and immunogenicity study in adults 18 to < 65 years old)
b. Study CSLCT-USF-07-41 (a non-inferiority immunogenicity and safety study in elderly adults ≥ 65 years old)
c. Study CSLCT-USF-07-36 (a non-inferiority immunogenicity and safety study in persons 6 months to < 18 years old)
d. Study CSLCT-USF-06-29 (an open label safety study in persons 6 months to < 18 years old).

Traditional approval will be based on the clinical reports from postmarketing studies CSLCT-USF-06-28 and CSLCT-USF-07-41 required to comply with the conditions specified in the September 28, 2007, original submission approval letter. The 2 additional required postmarketing pediatric studies specified in the September 28, 2007, approval letter were also included with this supplement. These studies were changed to postmarketing commitments following approval of CSL's pediatric efficacy supplement STN 125254/132 as noted in the August 30, 2010, FDA addendum approval letter for that supplement. Traditional approval in adults will extend traditional approval to the pediatric population.

Hemagglutination inhibition (HI) assay validation reports for A/Brisbane/59/2007 (H1N1) and B/Brisbane/60/2008 strains used in the studies were also included in this supplement. A validation report for a real-time reverse transcriptase polymerase chain reaction (real-time RT-PCR) assay used for influenza strain typing was also submitted as were Standard Operating Procedures (SOPs) and validation reports for influenza culture, typing and gene sequencing.

2. BACKGROUND

AFLURIA was approved for active immunization against influenza in adults ≥ 18 years of age on September 28, 2007 under accelerated approval regulations. Approval was based on immunogenicity and safety data from studies using a surrogate marker (HI antibody response) for clinical efficacy and 4 additional clinical studies were required to gain traditional approval. Accelerated approval was extended to children 6 months to < 18 years of age on November 10, 2009 (STN 125254/132) in response to the 2009 H1N1 influenza pandemic and the public health need for additional pediatric influenza vaccine. Pediatric approval was based on data from an open-label safety and immunogenicity study in children 6 months to 9 years old. The current supplement (STN 125254/259) was submitted on November 23, 2010, to support traditional approval of AFLURIA. Due to changes required to correct content and formatting issues with the provided data, the CBER receipt date was assigned February 1, 2011.

In April 2010, an increase in postmarketing reports of pediatric fever and febrile seizure events associated with the use of CSL's Fluvax (AFLURIA) in the Southern Hemisphere (SH) was observed. A similar increase was not observed for other trivalent influenza vaccines (TIVs) administered in the 2010 SH flu season. In response, the US Advisory Committee for Immunization Practices (ACIP) recommended on August 6, 2010, that AFLURIA not be used in persons < 9 years old and similar recommendations were issued in Australia, New Zealand and the European Union. A root cause investigation of the febrile events was inititated by CSL in April 2010. Also in April 2010, FDA inspected CSL's Australian manufacturing facilities and issued a Form FDA 483 to CSL citing significant current good manufacturing practice (CGMP) deviations. On July 30, 2010 FDA issued a postmarketing requirement (PMR) for CSL to conduct a prospective study to evaluate the risk of febrile events in pediatric subjects. On December 22, 2010, CSL submitted a good cause argument (STN 125254/271) indicating that it would be unable to fulfill FDA's July 30, 2010, PMR due to ethical, recruiting and product issues. FDA agreed with CSL and released them from this PMR on February 23, 2011.

Following another FDA inspection of CSL's Australian manufacturing facilities in March 2011, CSL was issued a Form FDA 483 and on June 15, 2011 FDA issued CSL a warning letter citing continued CGMP compliance deviations and an inadequate investigation into the root cause of the febrile events. FDA revised the use of AFLURIA from persons ≥ 6 months of age to persons ≥ 5 years of age on July 15, 2011 in its approval of CSL's 2011/2012 influenza strain change supplement STN 125254/303 because of a) the Fluvax (CSL's Southern hemisphere influenza vaccine formulation) associated 2010 febrile seizure signal, b) CSL's incomplete root cause investigation and c) because it was not feasible to enroll subjects 5-9 years of age in a PMR study because of recommendations that Afluria/Fluvax not be administered to children < 9 years of age. CSL is currently conducting 2 postmarketing pediatric surveillance studies of its current formulation of Fluvax (AFLURIA) in Australia and New Zealand.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

No manufacturing changes were proposed and no manufacturing information was submitted in this supplement.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

N/A

5. CLINICAL PHARMACOLOGY

N/A

6. CLINICAL/STATISTICAL

Studies submitted to support traditional approval:

- **Adult Efficacy Study (CSLCT-USF-06-28).** This was a phase 4, randomized, observer blind, multicenter, placebo-controlled study of the efficacy of AFLURIA in the prevention of culture-confirmed influenza illness conducted at 23 sites in Australia and New Zealand. The study was conducted during the 2008 and 2009 Southern Hemisphere influenza seasons in healthy adults 18 to 49 years of age.

- **Elderly Non-inferiority Study (CSLCT-USF-07-41).** This was a phase 4, randomized, observer blind, multicenter, comparator-controlled non-inferiority comparison study of AFLURIA versus a US-licensed inactivated split-virion vaccine (Fluzone) conducted at 21 sites in the US. The study was conducted during the 2008-2009 Northern Hemisphere influenza immunization season in healthy elderly adults 65 years of age or older.

In addition, pediatric non-inferiority and safety studies were also included in the submission:

- **Pediatric Non-inferiority Study (CSLCT-USF-07-36).** This was a Phase 3, randomized, observer blind, multicenter, comparator-controlled non-inferiority comparison of AFLURIA versus a US-licensed inactivated split-virion vaccine (Fluzone) conducted at 23 sites in the US. The study was conducted during the 2009-2010 Northern Hemisphere influenza immunization season in healthy children aged 6 months to < 18 years of age.

- **Pediatric Safety Study (CSLCT-USF-06-29).** This was a phase 4, multicenter, open-label safety study in healthy children 6 months to < 18 years of age conducted at 7 sites in Australia during the 2009-2010 Southern Hemisphere influenza season.

6.1 Efficacy and Immunogenicity

The efficacy of AFLURIA was assessed in study CSLCT-USF-06-28, a randomized, observer-blind, placebo-controlled study in 15,044 healthy adult volunteers 18 to 49 years of age conducted over 2 SH influenza seasons. Subjects were randomized 2:1 to receive AFLURIA or placebo, respectively. The study was designed to enroll 7500 subjects in 2008 and an additional 7500 subjects in 2009 if an interim analysis showed that the 2008 influenza attack rate for

vaccine matched strains was below 3%. The study was designed to provide 90% power. The study's primary objective was that vaccine efficacy would be demonstrated if the lower bound of the 1-sided confidence interval ($\alpha = 0.01387$, adjusted for the interim analysis) for the efficacy of vaccine versus placebo was $\geq 40\%$. The primary efficacy endpoint was the incidence of any laboratory-confirmed influenza A or B illness. The secondary efficacy endpoint was the incidence of laboratory-confirmed influenza A or B illness for strains matched to the vaccine strains.

Subjects with an influenza-like illness were identified by active and passive surveillance of nasal and throat swabs obtained from these subjects within three days of symptom onset beginning 14 days post vaccination and continuing until November 30 of that year or until the end of the influenza season. Influenza illness was confirmed by real-time RT-PCR and gene sequencing (for A strains) or pyrosequencing (for B strains).

The results for the primary and secondary efficacy endpoints are shown in Table 1.

Table 1. Study CSLCT-USF-06-28: Vaccine Efficacy for Per Protocol population for combined 2008 and 2009 seasons

Endpoint	Influenza Illness Incidence (%)		Vaccine Efficacy* (%)
	AFLURIA (n = 9889)	Placebo (n = 4960)	
Primary (any influenza strain)	2.24	3.87	42 (28)
Secondary (vaccine-matched influenza strains)	0.59	1.47	60 (41)

* The lower bound of the confidence interval is shown in parentheses and was adjusted to account for the interim analysis. Source: STN 125254/259/0, Module 5.3.5.1.3, p63, Table 11.3.

In relation to the study's primary endpoint, the efficacy of AFLURIA was 42% with a lower bound of 28%. This result did not meet the success criteria for demonstration of clinical efficacy as pre-defined in the study protocol. However, the primary endpoint for most influenza vaccine clinical trials is typically defined in relation to vaccine-matched strains, not any influenza strain. The criterion for success was met for the secondary efficacy endpoint with AFLURIA demonstrating an efficacy of 60% with a lower bound of 41%.

Immunogenicity analyses for each of the 3 influenza strains contained in the vaccine (H1N1, H3N2 and B) were performed on a subset of subjects from study CSLCT-USF-06-28 using samples collected on Study Day 0 and Day 21. Samples were collected from all subjects in 2008 and the first 450 subjects in 2009. Antibody titers were determined for ≈300 AFLURIA recipients and ≈150 placebo recipients for each of the 2 seasons. The study was designed with secondary immunogenicity endpoints of seroconversion rate (SCR, defined as the percentage of subjects with at least a 4-fold rise in HI antibody titers by Study Day 28) and the proportion of subjects with an HI antibody titer of $\geq$ 1:40 on Study Day 28. The SCR acceptance criterion was that the lower bound of the 95% confidence interval for the proportion of subjects achieving seroconversion should be $\geq 40\%$. The acceptance criterion for the proportion of subjects who achieved HI antibody titers of $\geq$ 1:40 on Study Day 28 was that the lower bound of the 95% confidence interval should be $\geq 70\%$. The results for study CSLCT-USF-06-28 show that the

SCR for AFLURIA recipients and the proportion of subjects with HI titers ≥ 1:40 after vaccination with AFLURIA met the criteria for demonstration of immunogenicity in the May 2007 FDA Guidance for Industry, "Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines." These results are shown in Table 2.

Table 2. Study CSLCT-USF-06-28: Immunogenicity Analysis of HI Assay Data for the Evaluable Population

Endpoint, strain	2008 Season		2009 Season	
	AFLURIA (n = 303)	Placebo (n = 147)	AFLURIA (n = 291)	Placebo (n = 149)
% Seroconversion*				
H1N1	80.9 (76.0)	0.7 (0.0)	77.7 (72.4)	0.7 (0.0)
H3N2	86.5 (82.1)	0.7 (0.0)	81.1 (76.1)	1.3 (0.2)
B	63.0 (57.3)	0.7 (0.0)	60.8 (55.0)	0
% HI titer ≥ 1:40				
H1N1	99.0 (97.1)	42.2 (34.1)	93.8 (90.4)	35.6 (27.9)
H3N2	96.7 (94.0)	34.7 (27.0)	93.8 (90.4)	43.0 (34.9)
B	76.9 (71.7)	12.9 (8.0)	89.3 (85.2)	30.2 (23.0)

* Values in parentheses are the lower bound of the 95% confidence interval.
Source: STN 125254/259/0, Module 5.3.5.1.3, p67, Table 11.4.

Immunogenicity analyses were also performed for the non-inferiority studies CSLCT-USF-07-41 and CSLCT-USF-07-36. CSLCT-USF-07-41 was conducted in 1268 adults ≥ 65 years old and CSLCT-USF-07-36 was conducted in 1474 children aged 6 months to < 18 years. Subjects in CSLCT-USF-07-36 were stratified into 3 age cohorts (6 months to < 3 years, 3 years to < 9 years and 9 years to < 18 years). Subjects were randomized 1:1 to receive either AFLURIA or the US-licensed influenza vaccine Fluzone in both studies. The co-primary endpoints for each study were SCRs and geometric mean titers (GMTs). There were 2 acceptance criteria for each study: 1) the upper bound of the 2-sided 95% CI on the difference between the Fluzone and AFLURIA SCRs did not exceed 10%, and 2) the upper bound of the 2-sided 95% CI for the ratio of the Fluzone geometric mean fold increase (GMFI) to AFLURIA GMFI did not exceed 1.5. The GMFI is defined as the GMT post-vaccination/GMT pre-vaccination. FDA requested post-hoc analysis using GMT ratios adjusted for baseline antibody titers. The results in the per protocol populations for the co-primary immunogenicity endpoints are shown in Table 3.

Table 3. Immunogenicity Results for Per Protocol Populations of Studies CSLCT-USF-07-41 and CSLCT-USF-07-36

Influenza Strain	GMFI		GMFI Ratio*	SCR		SCR difference*
	AFLURIA	Fluzone		AFLURIA	Fluzone	
CSLCT-USF-07-41						
H1N1	3.17	3.46	1.09 (1.25)	38.8	43.0	4.1 (9.6)
H3N2	7.11	7.15	1.00 (1.17)	69.4	68.7	-0.7 (4.5)
B	2.62	3.00	1.14 (1.29)	29.3	34.4	5.2 (10.4)
CSLCT-USF-07-36						
H1N1	9.68	8.55	0.88 (1.04)	70.2	66.0	-4.2 (0.8)
H3N2	11.12	11.67	1.05 (1.23)	74.9	76.9	1.9 (6.5)

Influenza Strain	GMFI		GMFI Ratio*	SCR		SCR difference*
	AFLURIA	Fluzone		AFLURIA	Fluzone	
CSLCT-USF-07-41						
B	8.08	7.56	0.94 (1.07)	69.3	70.6	1.3 (6.3)

* Values in parentheses are the upper bounds of the 95% confidence intervals.
Source: STN 125254/259/0, Module 5.3.5.1.3, Table 11.3, p52, Table 11.4, p55 (CSLCT-USF-07-41) and STN 125254/259/3, Module 5.3.5.1.3, Table 11.3, p61 (CSLCT-USF-07-36).

As shown above, all acceptance criteria for the per protocol population were met except for the B strain SCR criterion which was narrowly missed. Results for evaluable populations and for the post-hoc adjusted GMT ratios were similar. Results for study CSLCT-USF-07-41 based on a modified per protocol population were also calculated and were similar to the per protocol population. CBER-requested, post-hoc analysis of data for 5-18 year old subjects in study CSLCT-USF-07-36 showed that the B strain SCR acceptance criterion was not met (the upper bound of the 95% confidence interval was 11.4%). However, this was likely because the study was not powered for this age subset analysis.

In the opinion of the Clinical Reviewer, the results of studies CSLCT-USF-06-28 and CSLCT-USF-07-41 support traditional approval in the adult and elderly populations, respectively.

6.2 Biopharmaceutical Assays

Hemagglutination Inhibition (HI) Assay

HI assays were performed by ----------(b)(4)---------- to measure levels of influenza-specific serum antibodies to hemagglutinin (HA). Assessments of anti-HA antibody titers were performed for a subset of subjects in Study CSLCT-USF-06-28 and for all subjects in studies CSLCT-USF-07-41 and CSLCT-USF-07-36. --------(b)(4)-------- HI assay validation reports CTAVAL 119.019-6 and CTAVAL 119.019-16 for strains A/Brisbane/59/2007 (H1N1) and B/Brisbane/60/2008, respectively, were submitted with this supplement. The Product Reviewer found the reports to be acceptable. HI assay validation reports for the other influenza strains used in the clinical trials were previously submitted to the original BLA application (STN 125254/0) and to IND -(b)(4)- (serials 32 and 45) and were acceptable.

Influenza Virus Culture and Subtyping Assays

Nasopharyngeal and oropharyngeal swabs obtained from subjects meeting the clinical criteria for influenza-like illness were analyzed for influenza A/B identification by ---------(b)(4)---------- using a validated Influenza Virus Rapid Culture method and/or a validated influenza A/B real-time RT-PCR method. Characterization of influenza isolates in reference to their similarity with vaccine strains was performed by the World Health Organization Collaborating Center (WHO-CC) for Reference and Research on Influenza. Characterization was initially designed to be performed using HI assay and standard ferret antisera on samples provided by -------(b)(4)-------- to the WHO-CC. However, the protocol was subsequently revised (IND -(b)(4)-, Amendment 101) to include WHO-CC typing by RT-PCR and gene sequencing (A strains) or RT-PCR and pyrosequencing (B strains) since samples received by the WHO-CC in 2008 were non-viable and

could not be analyzed by HI assay but could be analyzed using the additional methods. No cause for the sample non-viability was determined. The revised protocol also specified that -(b)(4)---------- would perform conventional culture in the 2009 season on influenza positive samples to create backup material for typing if needed. Standard Operating Procedures (SOPs) and validation reports of the SOPs used for viral culture, typing and sub-typing included in this supplement are shown in Table 4. The SOPs and reports were reviewed by the Product and Biostatistics Reviewers and were found to be acceptable.

Table 4. STN 125254/259 validation reports and SOPs.

Validation Report/SOP	Description
TSOP.129.126	-------(b)(4)-------- SOP for PCR used for influenza typing (types A and B) in CSLCT-USF-06-28. Developed at -------(b)(4)---------.
TSOP.129.098	-------(b)(4)-------- SOP for PCR for influenza typing (types A and B)
AVAL.129.097	Comparability study (validation report) of TSOP.129.126 and TSOP.129.098
TSOP.129.183	SOP for influenza subtyping (2009 H1N1) used in CSLCT-USF-06-28 for samples testing positive by TSOP.129.126. Granted EUA in Aug 2009.
AVAL.129.156	Validation report for TSOP.129.183
WHO 052	Validation report for SOP WHO 049 (Spot Test for Identification of Influenza Isolates)
WHO 051	Validation report for SOP WHO 004 (Hemagglutination Inhibition Assay for Typing of Influenza Virus Isolates)
WHO 059	Validation report for SOP WHO 058 (Real-Time Reverse Transcriptase Polymerase Chain Reaction for Typing of Influenza Viruses)
WHO 061	Validation report for SOP WHO 057 (Gene Sequencing of the Haemagglutinin or HA1 Domain of Influenza AH1 or AH3)
WHO 060	Validation report for SOP WHO 056 [Pyrosequencing for Determining the Lineage of Influenza B Viruses (B/Victoria/2/87 or B/Yamagata/16/88)]
AVAL.115.072	Validation report for -------(b)(4)------- TSOP.115.102 (Influenza Virus Rapid Culture)
TSOP.115.195	Viral Culture Inoculation Procedure
TSOP.115.194	Viral Detection and Identification Procedure
MOL9100	Influenza A H1N1 (2009) Real Time RT-PCR test package insert
AVAL.129.156	Influenza A H1N1 (2009) RNA Real Time RT-PCR Assay

Source: STN 125254/259/0, Module 5.3.5.4 and STN 125254/259/4, Module 5.3.5.4

6.3 Pediatric Research Equity Act Requirements

Under the Pediatric Research Equity Act (PREA, 21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. Additionally, PREA-deferred studies submitted as a Biologics License

Application supplement must have a pediatric assessment completed and presented to the Pediatric Research Committee (PeRC). Because AFLURIA was approved for pediatric use on November 10, 2009 (STN 125254/132), the pediatric studies provided in this submission were changed from requirements to commitments. In addition, a waiver was granted for studies of AFLURIA in children < 6 months old following a PeRC review which occurred during the review of STN 125254/132. Thus, the current application was not presented to the PeRC.

6.4 Bioresearch Monitoring (BIMO) Inspection

---------- Removed Per Privacy Act ----------

---

7. SAFETY

7.1 Safety Data from Clinical Studies and Postmarketing Experience

Adults

The most common solicited adverse events (AEs) in the adult and the elderly studies CSLCT-USF-06-28 and CSLCT-USF-07-41 were injection site pain and tenderness, headache, malaise and myalgia. Fever was slightly more frequent in AFLURIA compared to placebo recipients (2.6% versus 1.9%, respectively) among adults 18 to < 65 years of age, while rates of fever in the elderly were low in both AFLURIA and Fluzone recipients (0.5% versus 0.6%, respectively). The frequencies of solicited AEs observed in these trials were similar to those for other trivalent influenza vaccines (TIVs).

Rates of severe adverse events (SAEs) were low but higher in the elderly than in younger adults (3.3% versus 1%, respectively). However, the types and rates of SAEs were similar between AFLURIA and control groups and the increased rates of SAEs in the elderly reflected the common medical conditions in that population. None of the SAEs or the 5 deaths occurring in the adult and elderly populations were considered to be related to AFLURIA.

Children

Data pooled from studies CSLCT-USF-07-36 and CSLCT-USF-06-29 showed that the most frequent solicited local AE in pediatric subjects was injection site pain of mild to moderate intensity and that the rates were similar between treatment groups (Source STN 125254/259.3, Module 1.11.3, RFI 10 March 2011-Qn 1-4, Tables 21 and 22, pg 35-36). In children 6 months to < 3 years of age, solicited systemic AEs of fever, nausea/vomiting, irritability and loss of appetite occurred, respectively, 2.3, 1.5, 1.2 and 1.2 times more frequently following the first

vaccination in AFLURIA than in Fluzone recipients. Rates of solicited systemic AEs following the second vaccination and in older age groups were lower and were similar between treatment groups.

Rates of severe solicited systemic AEs in children 6 months to < 3 years of age following the first vaccination were more frequent in AFLURIA (6.7%) than in Fluzone (2.6%) recipients.

The use of CSL's Southern Hemisphere trivalent influenza vaccine, Fluvax, was associated with a substantial increase in the reports of fever and febrile seizures in Australia beginning in April 2010. Most events occurred within 12 hours of vaccine administration and primarily in children < 5 years old with the majority of events occurring in children 1 to 2 years old. The rate of febrile seizures in Fluvax recipients was estimated to be 5 to 9 per 1000 vaccinations compared to 2009 Australian data estimates of 0 to 0.6 per 1000 vaccinations and US estimates from the CDC Vaccine Safety Datalink of 0.03 to 0.16 per 1000 vaccinations. Reports of febrile events such as vomiting, diarrhea, delirium and hallucinations occurring within 24 hours of vaccination were also increased in Fluvax recipients, predominantly in children < 5 years old.

FDA restricted the use of Afluria to above 5 years old on July 15, 2011 based on the increased rate of febrile seizures observed in post-marketing surveillance of the Fluvax 2010 SH formulation in Australia. FDA additionally requested that CSL perform a post-hoc analysis of study CSLCT-USF-07-36 data for persons 5 to 9 years old. This analysis showed that fever, high fever, nausea/vomiting and malaise occurred, respectively, 1.9, 4.1, 1.6 and 1.8 times more frequently following the first vaccination in AFLURIA compared to Fluzone recipients. However, because of the statistical limitations of this analysis, these results must be interpreted with caution.

In the opinion of the Clinical Reviewer, the use of AFLURIA should be further restricted to persons ≥ 9 years old for reasons outlined in the clinical review memorandum (refer to clinical review memorandum). The supervisor and Division Director did not concur with this recommendation and provided the rationale for not imposing this restriction in separate memoranda.

The postmarketing reports of increased incidence of fever and febrile seizures in pediatric subjects following administration of the 2010 Southern Hemisphere influenza vaccine (Fluvax) which had been considered "new safety information" as defined in 505-1(b)(3) of the Federal Food, Drug & Cosmetic Act had been already included in the AFLURIA product labeling in July 2010. In addition, the most recent regulatory action took place July 15, 2011 with the approval of CSL's annual strain change supplement STN 125254/303. Since then, no additional "new safety information" was available to CBER. Because section 505(o)(3) of the Act authorizes FDA to require postmarketing studies or clinical trials at the time of approval or after approval **only** in those situations where FDA becomes aware of "new safety information," no additional PMR in children 5- 9 years of age could be required.

7.2 Pharmacovigilance Plan and Pregnancy Registry

To address concerns regarding febrile seizures, CSL proposes conducting routine pharmacovigilance, enhancing passive surveillance using targeted questionnaires, conducting 2 active surveillance studies in the 2011 Southern Hemisphere influenza season and conducting laboratory investigations to determine a root cause for the 2010 SH febrile seizure signal. CSL also proposes conducting routine pharmacovigilance to monitor for rare, serious events and to monitor the use of the vaccine in pregnant women. The Pharmacovigilance Reviewer noted that neither of the 2 active surveillance studies is of sufficient size to evaluate any of the rare, serious outcomes listed in CSL's pharmacovigilance plan. In addition, studies to further address the safety of this product in pediatric subjects 5-9 years old are not feasible because of recommendations that Afluria/Fluvax not be administered to children < 9 years of age.

Due to the limited prelicensure and postlicensure data on the safety of AFLURIA in pregnant women, the Pharmacovigilance Reviewer recommends a postmarketing study to improve pregnancy surveillance. On November 14, 2011 (Amendment 11), CSL agreed to establish a pregnancy registry for AFLURIA and concurred with CBER's recommended timeline for establishing this registry.

8. ADVISORY COMMITTEE MEETING

It was determined that presentation of the supplement to the Vaccines and Related Biological Products Advisory Committee (VRBPAC) was not required because of the existing experience with the currently licensed AFLURIA vaccine. Additionally, review of the information submitted in this supplement did not raise concerns or controversial issues which would have benefited from an advisory committee discussion.

9. OTHER RELEVANT REGULATORY ISSUES

A warning letter was issued to CSL on June 15, 2011, as noted in the Background section above. However, since the information submitted in the current supplement contains data required by regulations as a condition of accelerated approval, the FDA Office of Compliance and Biologics Quality had no objection to the approval of this supplement.

10. LABELING

Revisions were made to the prescribing information to include the results of Studies CSLCT-USF-06-28, CSLCT-USF-07-36, CSLCT-USF-07-41 and CSLCT-USF-06-28. These revisions primarily involved Section 6.0 *Adverse Reactions* and Section 14.0 *Clinical Studies*. Additional revisions were made, where appropriate, to harmonize the AFLURIA label with other influenza vaccine labels.

After negotiations with the sponsor, it was determined by the committee that the prescribing information submitted in Amendment 13 (December 1, 2011) is acceptable.

11. RISK/BENEFIT ASSESSMENT AND RECOMMENDATIONS

Because the results of the clinical endpoint study demonstrated adequate effectiveness of AFLURIA, the accelerated approval commitment to verify clinical benefit was fulfilled.

In summary, the relevant safety, immunogenicity and clinical efficacy data from studies submitted in this BLA supplement will be included in the prescribing information and AFLURIA will be granted traditional approval at this time.

The committee recommends approval of this BLA supplement.