Afluria, Influenza Virus Vaccine
Prior Approval Supplement: Pediatric Indication
Clinical Review

1 General Information

1.1 Medical Officer's Review Identifiers and Dates

1.1.1 BLA Supplement: #125254/132

1.1.2 Related INDs and BLAs:

- IND-(b)(4)-
- STN #125254/0: Afluria [Influenza Virus Vaccine] approved September 28, 2007 for active immunization of persons ages 18 years and older against influenza disease caused by influenza virus subtypes A and type B present in the vaccine.

1.1.3 Reviewer Name, Division and Mail Code:

Clinical Reviewer: Cynthia Nolletti, MD
CBER/OVRR/DVRPA/Clinical Trials Branch
HFM-485
Supervisory Reviewer: Lewis Schrager, MD

1.1.4 Submission Received by FDA: September 11, 2009

1.1.5 Draft Review Completed: October 1, 2009
Final Review Completed: November 7, 2009

1.2 Product

1.2.1 Proper Name: Influenza Virus Vaccine
1.2.2 Trade Name: Afluria
1.2.3 Other Established or Proprietary Names:
Fluvax, Enzira, Influenza Vaccine-CSL Limited, and CSL Influenza Virus Vaccine (CSL IVV)

1.2.3 Product Formulation:

Active Ingredients: Each 0.5mL dose of the 2009-2010 trivalent vaccine contains HA from three influenza strains:

- A/Brisbane/59/2007 (H1N1) virus 15µg
- A/Uruguay/716/2007 (H3N2) virus 15µg
- B/Brisbane/60/2008 virus 15µg

Total 45µg HA antigen

(Note: A/Uruguay/716/2007 (H3N2) is a WHO-recommendedA/Brisbane/10/2007-like virus)

Adjuvants: none

The product is supplied in three presentations:

- Preservative-free single dose pre-filled syringe (0.5mL IVV)
- Preservative-free single dose pre-filled syringe (0.25mL IVV)
- Thimerosal-containing multi-dose vials
  Each 5mL vial contains 10 doses.
  Each 0.5mL dose contains 50μg thimerosal (24.5 μg mercury)

Excipients per 0.5mL dose:

- 50 μg of thimerosal (multidose vials only)*
- 4.1 mg sodium chloride
- 80 μg monobasic sodium phosphate
- 300 μg dibasic anhydrous sodium phosphate
- 20 μg monobasic potassium phosphate
- 20 μg potassium chloride
- 1.5 μg calcium chloride
- water for injection to 0.5mL

*The pre-filled syringe presentation is completely thimerosal-free. Thimerosal is introduced to the Final Bulk Vaccine so that the multi-dose presentation contains 0.01%w/v thimerosal to comply with 21 CFR 610.15 which states that products in multiple-dose containers shall contain a preservative.

1.3 Applicant: CSL, Limited (heretofore called "applicant" or "CSL")

1.4 Pharmacologic Class or Category: Vaccine

1.5 Proposed New Indication:

The current approved indication is for active immunization of persons 18 years of age and older against influenza disease caused by influenza virus subtypes A and type B present in the vaccine. With this supplement, the applicant is requesting approval to extend this same indication to persons 6 months of age and older.

1.6 Proposed Population(s): Persons 6 months of age and older.

1.7 Dosage Form and Route of Administration:

The current approved dosage form and route of administration is 45μg influenza antigen (15μg per strain) per 0.5mL dose administered intramuscularly.

With this supplement, the Applicant seeks approval:

- To extend the indication for the thimerosal-free pre-filled syringe (0.5mL) presentation to persons 3 years of age and older, and
- For a second thimerosal-free pre-filled syringe (0.25mL) presentation in children ≥ 6 months to < 3 years of age.

The route of administration will remain intramuscular for all age groups.

1.8 Revisions to the Package Insert:

With this Supplement, the Applicant has submitted a revised package insert and labeling for both the seasonal and pandemic Influenza A (H1N1) 2009 monovalent vaccines in the format required by FDA's Final Rule titled "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" published in January 2006.

2 Table of Contents

1. General Information……p. 1
2. Table of Contents……p. 3
3. Executive Summary……p. 5
4. Significant Findings from Other Review Disciplines……p. 6
5. Clinical and Regulatory Background…..……p.10
6. Clinical Data Sources, Review Strategy and Data Integrity……..p. 16
   - 6.1.1 BLA/IND volumes reviewed……p. 16
   - 6.1.2 Literature……p. 16
   - 6.1.3 Table of Clinical Studies……....p. 18
   - 6.1.4 Review Strategy……p. 19
7. Human Pharmacology……....p. 19
8. Clinical Studies……..p. 20
   - 8.1 CSLCT-FLU-04-05……...….p. 21
   - 8.1.1 Primary Vaccination – Overview……..……..…..p. 22
   - 8.1.2 Primary Vaccination - Results……...……p. 29
     - 8.1.2.1 Primary Vaccination – Population……....p. 29
     - 8.1.2.2 Primary Vaccination – Immunogenicity Results...……..p. 32
     - 8.1.2.3 Primary Vaccination – Safety Outcomes……p. 34
   - 8.1.3 Booster Vaccination ……p. 50
     - 8.1.3.1 Booster – Overview ……..…….....p. 50
     - 8.1.3.2.3 Booster – Immunogenicity Results……..…p. 52
     - 8.1.3.2.3 Booster – Safety Outcomes……....p. 53
   - 8.1.4 Comments and Conclusions CSLCT-FLU-04-05…….....p. 58
9. Overview of Efficacy Across Trials……..p. 63
10. Overview of Safety Across Trials……p. 66
11. Additional Clinical Issues...……..p. 76
12. Overall Conclusions……..p. 77
13. Recommendations……p. 78
    - 13.1 Approval……..p. 78

13.2 Recommendations on Post-Marketing Actions……...p. 79
13.3 Labeling……...p. 79
14. Appendix 1 ……p. 80

3 Executive Summary

The trivalent inactivated split virion egg-based influenza vaccine Afluria (CSL IVV) should be granted accelerated approval for the active immunization against influenza disease caused by influenza subtypes A and type B contained in the vaccine in persons 6 months of age and older. The recommendation to extend the current indication in adults 18 years and older to children and adolescents is based on data from an open-label study of 298 children 6 months to < 9 years of age placed in the context of a larger adult safety and immunogenicity database. The recommendation reflects a favorable assessment of potential benefit in the pediatric population.

This Prior Approval Supplement (PAS STN 125254/132) contains data from a single pediatric study, CSLCT-FLU-04-05. In this study (n=298), children 6 months to < 9 years of age met both immune response endpoints recommended in the FDA May 2007 Guidance for all three vaccine strains after receiving 2 doses of vaccine. Immune responses to the B strain were weaker relative to H1 and H3 strains, especially in children 6 months to 3 years of age, but the responses exceeded pre-specified endpoint criteria.

The safety database for children and adolescents consists primarily of data from CSLCT-FLU-04-05 in which 298 children 6 months to < 9 years of age were administered a total of 857 primary and booster doses of vaccine and were followed for 180 days after each dose. Injection site pain and erythema were the most common adverse events following vaccination. Younger children appear to experience relatively more fever and influenza-like symptoms than older children. Two serious adverse events (SAEs) possibly related to vaccination were reported: both were occurrences of fever and vomiting following a booster dose of vaccine. There were no deaths or discontinuations due to adverse events (AEs). No unusual new trends or safety signals were identified in the pediatric study CSLCT-FLU-04-05, in the interim Annual Report from a pediatric safety Post-Marketing Commitment (PMC), or in post-marketing surveillance from November 2002 to April 30, 2009.

The United States has faced a shortage of influenza vaccine since the fall of 2004 due to manufacturing challenges and to expanded recommendations for vaccination by the Advisory Committee for Immunization Practices (ACIP). In response to this shortage, on September 28, 2007, FDA granted accelerated approval to Afluria for active immunization of persons 18 years and older against influenza disease caused by influenza virus subtypes A and type B present in the vaccine. The recommendation for accelerated approval was based on demonstration of efficacy by a surrogate immune response endpoint in an adequate and well-controlled clinical trial. A randomized, placebo-controlled, double-blinded pivotal Phase III study showed that 1077 healthy adults randomized to receive CSL IVV had immune responses that exceeded the pre-specified immunogenicity endpoints. While there are no established correlates of immune protection for influenza, these pre-defined immune response criteria have a reasonable likelihood of predicting clinical efficacy. Four other European studies enrolled 652 subjects who received CSL IVV, 343 of whom were

65 years of age or older. These studies provided additional immune response data that supported an extension of the approved indication to adults 65 years of age and older.

The safety database for the original BLA STN 125254/0 included 29 clinical studies and post-marketing surveillance. The applicant reported a total of 4156 subjects exposed to CSL's trivalent influenza vaccine in the clinical safety database from 1992 to 2006, including 1376 subjects ≥ 60 years of age (900 of these were ≥ 65 years of age) and 298 children. Reported reactogenicity and unsolicited adverse events were typical for inactivated influenza vaccines. There were no unexpected or unusual trends, imbalances or safety signals.

CSLCT-FLU-04-05 was submitted to the original Afluria BLA in support of safety. Limitations of this pediatric study were the small sample size and the lack of a control group for safety. Although the original BLA contained efficacy data from adequate and well-controlled studies in the adult population that might be extrapolated to the pediatric population [21 CRF 314.55 (a), 21 CFR 601.41], the review team took a conservative approach and deferred approval of a pediatric indication pending additional data from post-marketing commitments.

Re-assessment of the risks and benefits of granting accelerated approval to Afluria in the pediatric population has been precipitated by two major factors. First, in 2008, the ACIP further expanded its recommendations for annual influenza vaccination to include children 5 to <18 years of age. Second, and of greater urgency, is the current 2009 H1N1 pandemic that has disproportionately affected children and young adults. At present, there is only one thimerosal-free seasonal inactivated trivalent influenza vaccine approved for use in children 6 months to 3 years of age. Accelerated approval of Afluria for use in children 6 months to < 18 years of age could expand the availability of a thimerosal-free seasonal influenza vaccine in this age group, especially in the youngest children at greatest risk for complications of influenza. Additionally, the regulatory pathway for approval of CSL's monovalent 2009 H1N1 pandemic vaccine in children could be facilitated by an approved seasonal vaccine in this age group.

Overall, the data submitted to this Prior Approval BLA Supplement suggests that Afluria is safe and immunogenic in children 6 months to < 9 years of age, and that Afluria has a favorable risk benefit ratio in children. Immunogenicity data can reasonably be extrapolated from the 3 to < 9 year and the > 18 year old age groups to children 9 to < 18 years of age. Therefore, based on the strength of the surrogate endpoint data and an acceptable safety profile, the clinical review team recommends that Afluria be granted accelerated approval in children 6 months to < 18 years of age because of potential clinical benefits that outweigh known risks. Post-marketing pediatric safety and non-inferiority studies, already in progress, will enhance the safety database in children, and will further support the efficacy data in this population.

4 Significant Findings from other Review Disciplines

4.1 Statistics – Please see the Statistics Review by Dr. Tammy Massie. The sample size of 300 was based on standards set by the Swedish Medical Products Agency specific to safety studies of influenza vaccine in pediatric populations. Due to the small sample size and lack of a comparator arm, this study was not designed or powered to perform inferential statistical tests. However, utilizing the data including immunogenicity and safety responses, descriptive statistics were computed and presented.

Dr. Massie's analyses found that the primary immunogenicity endpoints of seroconversion and proportion with a post-vaccination HI titer of ≥ 1:40 were met for all 3 influenza strains. Her review included analyses performed on the "full analysis" study population including all subjects receiving at least one dose of Afluria. These results were very similar to the sponsor's results from the "per protocol" analysis and provide reassurance that this product appears to provide sufficient immune response based on FDA recommendations. With respect to gender, Dr. Massie found that analysis of the immunogenicity endpoints yield similar results and conclusions regardless of gender. Dr. Massie concluded that the study vaccine met criteria for efficacy based on immune response and that the data is sufficient to support approval of Afluria in this age group.

4.2 Bioassay Review - Please see the Bioassay Review by Dr. Galina Vodeiko. The HAI assays for the pivotal study in the original BLA (CSLCT-FLU-05-09) were performed by ----------(b)(4)---------- conducted an HAI assay validation in 2006, and -(b)(4)- has performed the HAI assays for CSL since licensure in 2007. The (b)(4) assay validation was reviewed and approved by Dr. Sirota in 2007. Results of the (b)(4) Assay validation provided with this BLA supplement are, according to Dr. Vodeiko, the same as those approved in September 2007.

The HAI assays for the pediatric study CSLCT-04-05 were performed in 2005 by -------(b)(4)---------. CSL has submitted a technical transfer (proficiency) report rather than a true assay validation report for ---(b)(4)-- in this pediatric BLA supplement. The transfer report is a validation -------(b)(4)-------- of the HAI assay methodology from CSL to ---(b)(4)-- in 2003. Dr. Vodeiko noted some differences between the methods used in the (b)(4) assay as compared to the ---(b)(4)-- assay. Therefore, CSL was asked to clarify any changes made to the SOP since 2003 (Information Request dated October 16, 2009 and telecon on October 19, 2009).

The sponsor also submitted an Inter-Laboratory Comparability study to the sBLA. This study was undertaken to determine the degree of correlation between the HAI assay results from -------(b)(4)---------. The study used results from a panel of sera from 20 subjects in study CSLCT-NHF-05-13 (adults 18-60 years, 2006) that had been tested by both laboratories in 2006. The comparability study indicated that the HAI assay results from -------(b)(4)---------. correlate well. Dr.

Vodeiko also noted that the comparability study results for the H1 and H3 strains correlated well with respect to criteria determined by a 1994 international study investigating the reproducibility of influenza serological techniques (published by the National Institute for Biological Standards and Control, a WHO international laboratory in the UK). Dr. Vodeiko felt that the results of the Inter-Laboratory Comparability study supported approval of the HAI test transfer to --(b)(4)-- as long as the statistical assay review of this report by Dr. Sirota was acceptable.

4.3 **Statistical Assay Review** – Please see the Statistical Assay review by Dr. Lev Sirota and the summary of the Bioassay Review in Section 4.2 above. Dr. Sirota reviewed the same materials as Dr. Vodeiko: the (b)(4) HAI assay validation report, the -(b)(4)- technical transfer report, and the Inter-laboratory Comparability report. A telecon was held between FDA and CSL on October 19, 2009 to clarify questions regarding the technical transfer data and the Inter-laboratory Comparability data. CSL acknowledged that the ---(b)(4)---- data was actually proficiency data rather than a validation, and that they were very unlikely to succeed in obtaining any further details regarding the HAI assay from ---(b)(4)-------. Following CSL's response to the FDA IR of October 16, 2009 (STN 125254/132.3 and 132.4), Dr. Sirota concluded that the comparability study supported proportionality of results of the two laboratory assays, and, therefore, supported validity of the ---(b)(4)--- assay.

Dr. Tsai-Lien Lin, Acting Team Leader for the Viral and Bioassay Team, also evaluated the ----------(b)(4)---------- for OBE. Her comments are as follows:

"[CBER] asked the applicant to provide rationale for the acceptance criterion that the 95% confidence interval for the intercept should include the value of 1.0. The applicant presented an algebraic derivation showing that the perfect agreement regression line on the log-transformed scale has a slope of 1.0 and an intercept of 1.0 as well….

CSL's rationale for their intercept acceptance criterion is based on an incorrect algebraic derivation. Perfect agreement between the two laboratories would imply a regression line, on the logarithmic scale, with slope=1.0 and intercept=0 (i.e., a 45° line through the origin).

The applicant's linear regression analysis on the log-transformed HAI titer data of (b)(4) (Y) versus -(b)(4)- (X) showed that both estimated slope and intercept are near 1.0. With a slope near 1.0, relative proportionality is demonstrated, but an intercept near 1.0 suggests apparent bias between the two laboratories, i.e., (b)(4) consistently generates higher titer values than -(b)(4)-.

As long as there is relative proportionality, the immunogenicity statistic Seroconversion Rate (SCR) will still be reliable enough and not affected much by the bias, because fold-rise on the log scale is the distance between an individual data value and the cutoff value. When the slope is 1, the distance is the same for

both ---(b)(4)--- (X) and (b)(4) (Y). However, the Seroprotection Rate (SPR) can be affected to a larger extent, because this metric is based solely on the immune response meeting a specified threshold. Nevertheless, since -(b)(4)- assay has been fully validated and ---(b)(4)--- HAI results tend to be lower than --(b)(4)--, the SPR based on --(b)(4)-- assay data will generally be underestimated, if we view (b)(4) results as the true values. Therefore, the relative bias being in the conservative direction for --(b)(4)-- implies that the observed bias need not pose a concern to CBER. That is, if the immunogenicity results generated by --(b)(4)-- meet the CBER threshold criteria, they should meet the criteria had (b)(4) performed the assays."

In view of the statistical and bioassay reviewers' conclusions, the review team and Dr. Norman Baylor found the --*(b)(4)*-- HAI assay results to be acceptable.

4.3 CMC Review

Galina Vodeiko, Ph.D reviewed the one addition made to the CMC portion of the original BLA submission: the formulation of thimerosal-free 0.25mL pre-filled syringe seasonal trivalent and H1N1 monovalent vaccine presentations for use in children 3 months through 35 months of age.

Dr. Vodeiko found that no changes were made to drug substance, and that only minor changes were made to dispensing of the final bulk drug product. Composition of the drug product, specifications, batch analysis and consistency were acceptable. Long term data from stability testing for the Parkville and -*(b)(4)*- sites were acceptable. It was recommended that ongoing and planned stability testing for the --*(b)(4)*--- site including that for the H1N1 2009 monovalent vaccine be made a post-marketing commitment.

4.5 Facilities Review – Office of Compliance and Biologics Quality/Division of Manufacturing and Product Quality (OCBQ/DMPQ)

James Crim, OCBQ/DMPQ, reviewed the manufacturing changes and validation of processes made at the ------*(b)(4)*-------- facility to accommodate filling of the 0.25mL pre-filled syringe presentation. The modifications and validations were found to be acceptable.

Deborah Trout, OCBQ/DMPQ, reviewed the modifications and validation of processes made at the ----*(b)(4)*---- facility to accommodate filling of the 0.25mL pre-filled syringe presentation. The modifications and validations were found to be acceptable.

4.6 Advertising and Promotional Labeling

Please see the review memo by Catherine Miller regarding recommended changes to the Package Inserts and labeling for the cartons and containers.

5 Clinical and Regulatory Background

5.1 Disease or Health-Related Conditions Studied and Available Interventions

Influenza continues to be one of the greatest infectious causes of death in the United States and throughout the world, with mortality rates of 17,000 to 51,000 persons (mean 36,000) in the U.S. and 250,000 to 500,000 persons worldwide each year. It is responsible for more deaths in the U.S. than all other vaccine-preventable diseases combined. In the U.S., mortality from influenza increased from 1990 to 1999, and annual influenza-associated hospitalizations ranged from 55,000 to 431,000.

Influenza is caused by RNA viruses of the family Orthomyxoviridae. Two types, influenza A and influenza B, cause the vast majority of human disease. Influenza A is further categorized into subtypes on the basis of two principle surface antigens, hemagglutinin (HA) and neuraminidase (NA), which comprise the viral glycoprotein coat. There are multiple subtypes of Influenza A based on combinations of 16 variants of HA and 9 variants of NA, but only the subtypes H1N1, H2N2, and H3N2 appear to circulate in humans. In addition to humans, Influenza A has been isolated from non-human species including birds, horses, and swine. Influenza B is comprised of single HA and NA subtypes, and is known to occur only in humans. Antibodies to the surface antigens are subtype and strain-specific, and confer protection against future infection with identical strains, but not against another type or subtype.

Since 1977, influenza A subtypes H1N1 and H3N2 and influenza B have 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. These new strains are capable of causing epidemics because antibody resulting from prior exposure or vaccination is generally not protective. Larger antigenic changes result from multiple recombinant and reassortment events between hemagglutinin from co-circulating human or animal influenza A strains. These reassortment events occur less frequently, but result in antigenic shifts or new subtypes which are associated with pandemics. In this situation, large segments of the world's population have no pre-existing protective immunity to the new viral type or subtype. Illustrating this point is the emergence in April 2009 of a novel influenza A (H1N1) of swine origin. This virus is a reassortant containing genes from human, swine (North American and Eurasian lineages) and avian influenza viruses, and has resulted in a new pandemic.

Antigenic variants or strain changes occur each year necessitating yearly change in the formulation of the trivalent influenza vaccine for optimal protection. Neutralizing antibody (NA) against HA is the primary immune defense against infection with influenza. Although there is no established immune correlate of protection, anti-hemagglutinin antibody (HI) titers of 1:32 to 1:40 represent a

level at which approximately 50% of individuals will be protected. This strain-specific immune response appears to predict a clinical endpoint of efficacy with reasonable certainty. Previous experience with inactivated trivalent influenza vaccines suggests that HI titers might be used as a surrogate endpoint.

Influenza A and B causes illness in approximately 5% to 10% of adults annually (approximately 48 million persons in the U.S.) with higher attack rates in children. The highest rates of illness occur among 5-14 year olds, while the highest rates of serious illness and mortality are found among children < 2 years of age, adults ≥ 65 years of age, and persons with medical conditions placing them at increased risk for complications of influenza. Approximately 226,000 excess hospitalizations per year are attributed to influenza, with 63% occurring in persons ≥ 65 years of age. More than 90% of deaths occur in persons 65 years or older.

Children comprise an important component of influenza epidemiology. They contribute significantly to transmission. Influenza –like illness is the cause of as many as 20-30% of visits to healthcare providers in children < 5 years of age. Although pediatric deaths due to influenza are uncommon (0.4 per 100,000 children < 5 years in one study), most of these children have no underlying medical conditions. Since 2006-2007, there has been an increase in pediatric deaths due to complicating *Staphylococcus aureus* pneumonia in children with influenza. Regarding the novel pandemic 2009 H1N1 influenza virus, from mid-April to August 30, a total of 9,079 hospitalizations and 593 deaths associated with the 2009 pandemic H1N1 virus in the US were reported to the CDC. Forty-seven of these deaths occurred in the pediatric population.

Available interventions for controlling influenza include immunoprophylaxis and both prophylaxis and treatment with antiviral agents. Four licensed antiviral agents are available in the United States, but treatment is complicated by increasing resistance, adverse drug reactions, and the need for dose adjustments in children and renal insufficiency. In addition, the effectiveness of these drugs in preventing complications of influenza or in treating serious illness in hospitalized patients remains uncertain.

The primary mode of controlling influenza disease remains immunoprophylaxis. In view of the potential for serious and life-threatening influenza-related disease, the Centers for Disease Control and Prevention's (CDC's) Advisory Committee on Immunization Practices (ACIP) has, in recent years, broadened their recommendations for persons in whom annual influenza vaccination is recommended to include children 6 months to 18 years of age, pregnant women, and persons 50 years of age and older.

Vaccine efficacy is dependent on a number of variables including age and host immunity. When vaccine and circulating viruses are antigenically well-matched, vaccination with TIV has traditionally been estimated to be approximately 70-

90% effective in preventing influenza illness among young healthy adults < 65 years of age. Efficacy is lower among persons with underlying illnesses, those ≥ 65 years of age, or when there is a poor antigenic match between vaccine and circulating influenza virus strains. However, immunization may prevent influenza-related hospitalization or pneumonia in these populations. The efficacy of TIV in children has ranged from 54% to 100% in various studies, with some studies indicating lower efficacy against Influenza B. Culture confirmation studies of LAIV in children have demonstrated absolute efficacy of 90% or greater.

5.2 Important Information from Pharmacologically Related Products, Including Marketed Products

There are currently five licensed trivalent inactivated influenza vaccines in the United States: Afluria (CSL), Fluarix (GSK), FluLaval (GSK**,** formerly ID Biomedical), Fluvirin (Novartis, formerly Chiron), and Fluzone (sanofi pasteur). These are approved for use in adults. In addition, Fluvirin is approved for use in children 4 years of age and older, and Fluzone is approved for use in persons 6 months of age and older. Fluarix has just recently been approved in children ages 3 to 18. FluLaval does not have a pediatric indication. Fluarix and FluLaval do not have a pediatric indication. FluMist (MedImmune) is the only licensed live attenuated influenza vaccine (LAIV) in the U.S., and is currently approved for use only in healthy non-pregnant persons aged 2 to 49 years.

5.3 Previous Human Experience with the Product Including Foreign Experience

CSL first began manufacturing trivalent inactivated influenza vaccine in 1968. The thimerosal-containing vaccine was initially distributed in Australia and New Zealand from 1968 to 1984. During this period, changes in the manufacturing process included changing the inactivation agent from formaldehyde to beta-propiolactone and changing the disruption agent from sodium deoxycholate to sodium taurodeoxycholate. The vaccine then became authorized in 15 countries, and approximately 24 million doses of thimerosal-containing vaccine were distributed globally between 1985 and 2002. In November 2002 CSL IVV was replaced by a thimerosal-free product that was otherwise unchanged. CSL's thimerosal-free pre-filled syringe presentation was licensed for persons 6 months of age and older by the Australian Therapeutic Goods Administration (TGA) in November 2002 under the tradename Fluvax. Since 2002 CSL has distributed approximately ---(b)(4)--- thimerosal-free doses of vaccine worldwide, primarily in Australia, the United States and Europe. CSL's IVV is currently registered in 26 countries outside the US. In Europe, CSL IVV is also licensed in persons 6 months of age and older.

The safety database for the original BLA STN 125254/0 included 29 clinical studies and post-marketing surveillance:

- The pivotal Phase III study CSLCT-FLU-05-09 conducted in the US under BB-IND-(b)(4)-;
- The four supporting non-IND studies: CSLCT-NHF-05-15; CSLCT-NHF-05-11; CSLCT-NHF-05-13; and CSLCT-NHF-04-99;
- The pediatric study CSLCT-FLU-04-05;
- 23 older studies conducted in the Australia between 1992 and 2000, and;
- Post-marketing surveillance experience since 1985. This included approximately ---(b)(4)--- thimerosal-containing vaccine doses distributed from June 1997 to July 2002 and approximately ---(b)(4)--- thimerosal-free doses distributed from November 2002 to April 2006.

In the original BLA, the applicant reported a total of 4156 subjects exposed to CSL's trivalent influenza vaccine in the clinical safety database from 1992 to 2006, including 1376 subjects ≥ 60 years of age (900 subjects ≥ 65 years of age) and 298 children. The most common reactogenicity events reported among the studies submitted to the BLA and the integrated summaries of previous clinical trials were injection site pain, tenderness, and erythema, and headache, malaise, and myalgia. Common unsolicited adverse events included headache, nasal congestion, rhinorrhea, cough, and pharyngolaryngeal pain. Please refer to the original BLA review for details of the previously reviewed safety and immunogenicity data.

Prior to the pivotal study CSLCT-FLU-05-09 conducted under U.S. IND (b)(4), the applicant conducted four non-IND studies in the UK for the purpose of providing safety and immune response data for annual influenza vaccine antigen changes required by the European Union for annual registration:

- CSLCT-NHF-05-11, CSLCT-NHF-05-13, and CSLCT-NHF-04-99 stratified subjects into two groups: ≥ 18 to < 60 and ≥ 60 years of age.
- The fourth non-IND study, CSLCT-NHF-05-15, evaluated subjects ≥ 65 years.

In addition to the adult studies, the applicant conducted a fifth non-IND study in Australia in a pediatric population age 6 months to 9 years of age. CSLCT-FLU-04-05 was submitted to the original BLA to support the safety database. Although not specifically requested, summaries of immunogenicity data in tabular form and source data consisting of line listings for this study were also presented by the Applicant.

5.4 Regulatory Background Information (FDA-Sponsor Meetings, Advisory Committee Meetings, Commitments)

Please refer to the Clinical Review of the original Afluria BLA STN 125254/0 for details of the regulatory history.

2004: In the fall of 2004, the U.S. faced a shortage of influenza vaccine when one of only two manufacturers of U.S. licensed trivalent influenza vaccine experienced manufacturing problems. FDA responded by developing a "Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines," (final version May 2007), that defined regulatory pathways for licensure of trivalent inactivated influenza vaccine including guidance on an accelerated approval pathway. The guidance is based on The Code of Federal Regulations (CFR) subpart H 21CFR314.500, 21CFR314.510, and 21CFR601.41 which describe the indications and mechanisms for granting accelerated approval of new drugs on the basis of a surrogate endpoint for a serious or life-threatening condition when there is an unmet clinical need.

2006: On June 28, 2006, DHHS/CDC published the recommendations of the Advisory Committee on Immunization Practices (ACIP) for the prevention and control of influenza. The ACIP recommended that approximately 218.1 million individuals in the US (approximately 70% of the population) be included in the target group of individuals who should receive influenza vaccination. The initial recommendations targeted high risk individuals, their caregivers, and household contacts.

September 28, 2007: In the face of a continued shortage of influenza vaccine relative to expanded ACIP recommendations, Afluria was granted accelerated approval for active immunization of persons 18 years and older against influenza disease caused by influenza virus subtypes A and type B present in the vaccine.

2008: On February 27, 2008 (published in the MMWR July 17, 2008), the Advisory Committee on Immunization Practices (ACIP) voted to expand influenza vaccination recommendations to include all children 6 months to 18 years of age, beginning with the 2008-2009 season if feasible, but no later than the 2009-2010 influenza season. Future directions include the possibility of universal vaccination which will require 300 million doses of influenza vaccine. A national objective for 2010 is achieving 90% influenza vaccine coverage for persons $\geq$ 65 years of age and in residents of nursing homes regardless of age. Increasing coverage among those with high risk conditions including children has also been given highest priority. Goals for expanding influenza vaccine coverage among all age groups, and the threat of pandemics with either a novel strain of seasonal or avian influenza have lead to requests for use of the accelerated approval mechanism in order to increase the available supply of influenza vaccine.

April 2009: In response to the emergence of the novel 2009 H1N1 pandemic in April 2009, manufacturers of influenza vaccines have worked urgently with public health officials, clinical trial investigators, and regulatory authorities around the world to develop and expedite manufacture of a monovalent H1N1 vaccine in addition to the seasonal trivalent influenza vaccine. Recognizing the

need to expand the supply of thimerosal-free influenza vaccine (both seasonal and pandemic) in the pediatric population, especially in children 6 months to < 2 years of age where only one vaccine is licensed, FDA engaged CSL, Ltd in discussions to explore the possibility of extending licensure of Afluria to persons 6 months of age and older.

July 15, 2009: A teleconference was held on July 15, 2009 in which CBER requested that CSL submit a proposal for pediatric licensure of Afluria. This proposal was submitted to FDA on August 10, 2009, and a second teleconference was held on August 12, 2009 between FDA, CSL, and representatives from the Office of the Biomedical Advance Research and Development Authority (BARDA) to discuss CSL's proposal. FDA indicated that CSL could consider submitting a BLA supplement to support the use of Afluria in children and adolescents 6 months and older. The supplement would include the complete study report and original source data from study CSLCT-FLU-04-05. If approved, the supplement would support accelerated approval of both seasonal trivalent Afluria and a CSL's Monovalent 2009 H1N1 pandemic vaccine in children. FDA indicated that the ongoing adult culture confirmation study in healthy adults, CSLCT-USF-06-28, could be used to verify clinical benefit of the surrogate endpoint in children (21 CFR 601.41). Traditional approval would be contingent upon completion of the post-marketing commitments (PMCs) outlined in the original Afluria approval letter.

September 11, 2009: The Prior Approval Supplement (PAS) for seasonal Afluria was received by FDA on September 11, 2009.

Additional regulatory milestones:

- August 24, 2009 – Two dose-finding and safety studies of CSL's monovalent H1N1 vaccine were initiated (protocols submitted to IND --(b)(4)--:

    - CSLCT-CAL-09-61: "A Phase II, Multicenter, Randomized, Observer-Blind Placebo-Controlled Study to Evaluate the Immunogenicity, Safety and Tolerability of CSL's 2009 H1N1 Influenza Vaccine (CSL425) in Healthy Adults Aged 18 Years and Older"

    - CSLCT-CAL-09-62: "A Phase II, Multicenter, Randomized, Observer-blind, Placebo-Controlled Study to Evaluate the Immunogenicity, Safety and Tolerability of CSL's 2009 H1N1 Influenza Vaccine (CSL425) in a Healthy Pediatric Population".

- August 26, 2009 – Strain Change Supplement to the Afluria license (STN 125254/127) to extend the indication to include the active immunization of persons ages 18 years and older against influenza disease caused by the pandemic (H1N1) 2009 virus present in the vaccine.

- September 15, 2009 – FDA approved CSL's Influenza A (H1N1) 2009 Monovalent Vaccine for prophylaxis against the pandemic H1N1 in persons 18 years of age and older.

- September 2009 – A second supplement was submitted to the Afluria BLA requesting that the pediatric indication be extended to include active immunization of persons ages 6 months and older against influenza disease caused by the pandemic (H1N1) virus present in the vaccine. This approval will depend on approval of the current PAS STN 125254/132 under review.

- Vaccines and Related Biological Products Advisory Committee (VRBPAC) – A VRBPAC meeting was not felt to be necessary for the original Afluria approval in 2007 because the vaccine is a traditional trivalent influenza product, and there were no novel issues that required additional expert advice. Similarly, consultation with the VRBPAC will not be necessary for accelerated approval of the pediatric indication.

6 Clinical Data Sources, Review Strategy, and Data Integrity

6.1 Material Reviewed

6.1.1 BLA submission STN 125254/132 served as the basis for the Clinical Review:

- Module 1 Volume 1: Administrative information, labeling
- Module 2 Volume 1: Clinical Summary of Safety and Efficacy
- Module 5 Volumes 1-5: Complete Study Reports for CSLCT-FLU-04-05 the pivotal pediatric open label Primary Vaccination and Booster Dose studies; Case Report Forms, SAE Report Forms, Post-Marketing Reports, and literature.
- Amendment 125254/132.2: labeling.

- References to review of the original BLA summary and source data (line listings for safety data) for study CSLCT-FLU-04-05 where relevant are made in the body of this review.

6.1.2 Literature

- Belongia, EA, et al. Effectiveness of inactivated influenza vaccines varied substantially with antigenic match from the 2004-2005 season to the 2006-2007 season. J Infect Dis. 2009;199:159-167.

- Bhat N, et al. Influenza-associated deaths among children in the United States, 2003-2004. N Engl J Med 2005;353:2559-67.

- Bridges CB, et al. Inactivated Influenza Vaccines. In Plotkin S, Orenstein W, Offit P (eds). Vaccine. ____: Elsevier; 2008, 259-290.

- Centers for Disease Control and Prevention. H1N1 Flu. Accessed at http://www.cdc.gov/h1n1flu.

- Centers for Disease Control and Prevention. CDC Weekly H1N1 Flu Update. Accessed at http://www.flu.gov.

- Centers for Disease Control and Prevention. Prevention and Control of Influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2008 (Early Release July 17, 2008); 57(RR-7): 1-60.

- Centers for Disease Control and Prevention. Update: Influenza Activity – United States, April-August 2009. MMWR 2009; 58(36): 1009-1012.

- Centers for Disease Control and Prevention. Prevention and Control of Influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2009; 58(RR-8): 1-52.

- Centers for Disease Control and Prevention. Update: Influenza Activity-United States, September 28, 2008-April 4, 2009, and Composition of the 2009-2010 Influenza Vaccine. MMWR 2009; 58(14):369-374.

- FDA Guidance Document for Industry: "Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines" May 2007, which can be found on the World Wide Web at http://www.fda.gov/cber/gdlns/trifluvac.htm.

- Hobson, D, Curry, RL, Beare, AS, Ward-Gardner, A. The role of serum haemagglutinin-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. Journal of Hygiene, (Camb). 1972; 70: 767-777.

- Jackson, LA. Using surveillance to evaluate influenza vaccine effectiveness. J Infect Dis 2009; 199:155-158.

- Monto AS, Ohmit SE, et al. Comparative Efficacy of Inactivated and Live Attenuated Influenza Vaccines. N Engl J Med 2009; 361:1260-1267.

- Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team. Emergence of a Novel Swine-Origin Influenza A (H1N1) Virus in Humans. New Eng J Med 2009;(360): 2605-2615.

- Schrag SJ, et al. Multistate surveillance for laboratory-confirmed, influenza-associated hospitalizations in children, 2003-2004. Pediatr Infect Dis J 2006;25:395-400.

- Skowronski, DM, et al. Component-specific effectiveness of trivalent influenza vaccine as monitored through a sentinel surveillance network in Canada, 2006-2007. J Infect Dis 2009; 199:168-179.

- Thompson WW, et al. Influenza-associated hospitalizations in the United States. JAMA 2004;292:1333-40.

- Treanor, John J. Influenza Virus. In: Mandell, G., ed. Principles And Practice of Infectious Diseases. Philadelphia, PA: Elsevier, Inc.; 2005.

6.1.3 Post-Marketing Experience

The post-marketing experience in countries where CSL has marketing authorization for CSL IVV was summarized by the applicant in Module 2 (Sections 2.5.5 and 2.7.4.6) and Module 5 (Section 5.3.6). Data was derived from spontaneous adverse event reports received for CSL's thimerosal-free IVV. The data is included in CSL's Global Pharmacovigilence Database and covers an estimated ---(b)(4)--- doses distributed worldwide from November 2002 to April 2009. Periodic Safety Update Reports (PSURs) were provided to global regulatory authorities and are found in Module 5. Review of the post-marketing experience is found in Section 10 of this PAS review, Overview of Safety Across Trials.

6.2 Table of Clinical Studies

Data from one clinical study, CSLCT-FLU-04-05, both the Primary Vaccination and Booster Dose phases were submitted in support of the pediatric indication. To place this study in the context of the adult studies submitted in support of the original license application, the following table of primary studies submitted to the original BLA, including CSLCT-FLU-04-05, is provided below:

Table 6-1 Clinical Studies - Pediatric Approval Supplement and Original BLA

Study/ Date	Age Group	N**	US IND/ Sites	Phase	Design
CSLCT-FLU-04-05 Mar-Jul 2005 (both PAS and BLA)*	≥6mos <3yr ≥3yr to<9yr	151 147	No Australia	III	Open label Unblinded Uncontrolled
Adult Studies Supporting Original BLA					
CSLCT-FLU-05-09 Jun-Aug 2006	18to<65	1089	Yes 9 USA	III	Randomized 1:1:1:1:1 Double blinded Placebo control
CSLCT-NHF-05-15 Oct-Dec 2006	≥65	206	No UK**	IV	Randomized 3:1 Observer blind Influsplit control
CSLCT-NHF-05-11 Oct-Nov 2005	18to<60 ≥60	102 104	No UK	IV	Randomized 1:1 Observer blind

Study/ Date	Age Group	N**	US IND/ Sites	Phase	Design
					Mutagrip control
CSLCT-NHF-05-13 May-Jun 2006	18to <60 ≥60	60 60	No UK	IV	Open label Uncontrolled
CSLCT-NHF-04-99 May-Jun 2005	18to <60 ≥60	60 60	No UK	III	Open label Uncontrolled

*CSLCT-FLU-04-05 was submitted to the original BLA as supportive safety data
**N=number of subjects who received CSL IVV in each study

6.3 Review Strategy

For regulatory decisions regarding approval of Afluria in the pediatric age group 6 months to < 18 years, the immunogenicity and safety data from the primary vaccination phase of CSLCT-FLU-04-05 should be adequate to support licensure. However, the Applicant also provided safety and immunogenicity data from booster vaccinations in the second year of study CSLCT-04-05. These data were considered supportive and will be presented in this review. Data from the adult studies submitted to the original BLA is also considered supportive, and the reader is referred to the Clinical Review for STN 125254/0.

Data from the clinical study report, the integrated summaries of efficacy and safety, summary tables, and electronic datasets were reviewed and compared. The rates of adverse events were calculated from the datasets with special attention to hypersensitivity, immunologic and neurologic events of interest. Case report forms, SAE forms and spontaneous post-marketing adverse event reports were reviewed. The Statistical Reviewer was asked to analyze the immunogenicity datasets and these results were compared to the Applicant's report.

6.4 Good Clinical Practices and Data Integrity

Clinical studies conducted in Australia, including the pediatric studies and earlier studies up until 2005, were conducted under the Therapeutic Goods Administration (TGA) Clinical Trial Notification (CTN) Scheme and in accordance with TGA Guidelines for Good Clinical Research Practice, 1991.

6.5 Financial Disclosures

Financial disclosure statements for the two principal site investigators, Terry M. Nolan, MD and Peter C. Richmond, MD, are included in Module 1, Section 1.3.1.4. No conflicting financial arrangements or interests are disclosed.

7 Human Pharmacology

Exposure to influenza elicits a humoral immune response characterized by the development of antibodies to the major structural surface glycoproteins hemagglutinin (HA) and neuraminidase (NA). Antibodies to HA are best studied

and have been used as surrogate endpoints in clinical trials. Although no exact correlate of protection has been identified, serum HI titers of 1:40 or greater have been associated with protection against influenza in up to 50% of subjects.

Protection is primarily strain specific. Antibody against one influenza virus type or subtype confers limited or no protection against another. Depending on the degree of antigenic drift, antibody to one strain may or may not protect against an antigenic variant within the same type or subtype. Development of antigenic variants through antigenic drift in the HA and/or NA glycoproteins each year or every few years is the virologic basis for seasonal epidemics. The WHO usually recommends a change in one or more of the three influenza vaccine antigenic strains each year for optimal protection.

8 Clinical Studies

CSLCT-FLU-04-05

Efficacy assessments

The clinical studies with CSL IVV have assessed humoral immunogenicity primarily using the HI assay, and clinical endpoint studies of efficacy are in progress. The FDA Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines: May 2007, has indicated that for the purposes of accelerated approval of trivalent inactivated influenza vaccines, the HI antibody response may be an acceptable surrogate marker of activity that is reasonably likely to predict clinical benefit. A clinical endpoint efficacy study that assesses influenza illness as the primary endpoint in non-at risk adults is being conducted post-licensure in accordance with 21CRF 601.41.

CSLCT-FLU-04-05 was designed with primary endpoints based on the Committee for Proprietary Medicinal Products (CPMP) criteria (CPMP/BWP/214/96 Note for Guidance on Harmonization of Requirements for Influenza Vaccines) which are less stringent than FDA criteria as outlined in the FDA guidance. The major differences between these criteria are as follows:

- FDA criteria focus on the proportion of subjects who achieve a four-fold increase in HI titer to a minimum of 1:40 (referred to by FDA as the seroconversion rate) and the proportion of subjects with a minimum HI titer of 1:40 (referred to by some as “seroprotection”) while the CPMP includes the post-vaccination fold increase in geometric mean titer (GMT) from baseline as an additional criterion;

- Endpoints for the CPMP are based on point estimates of immunogenicity while the FDA endpoints are based on the lower bound of the 95% Confidence Interval (CI) of the estimates; and

- Successful fulfillment of the CPMP criteria depends on achieving at least one of the three immunogenicity endpoints for each strain, whereas FDA criteria requires that both the seroconversion rate and post-vaccination anti-HI antibody titer endpoints be met for all three strains.

For the purposes of this review, we will present immunogenicity data that is recommended in the FDA guidance criteria for immune response. No criteria for adequate responses have been developed for the pediatric population. We will therefore apply the FDA Guidance Criteria developed for adults < 65 years of age to the pediatric population in study CSLCT-FLU-04-05.

FDA Guidance Criteria:

- For adults < 65 years of age:
  - The lower bound of the two-sided 95% CI for the percent of subjects achieving a four-fold increase in HI antibody titer to a minimum of 1:40 (seroconversion rate) should meet or exceed 40%.
  - The lower bound of the two-sided 95% CI for the percent of subjects achieving an HI antibody titer ≥ 1:40 should meet or exceed 70%.

- For adults ≥ 65 years of age:
  - The lower bound of the two-sided 95% CI for the percent of subjects achieving a four-fold increase in HI antibody titer to a minimum of 1:40 should meet or exceed 30%.
  - The lower bound of the two-sided 95% CI for the percent of subjects achieving an HI antibody titer ≥ 1:40 should meet or exceed 60%.

HI Assay Validation

Please see Section 9.2 of this review and Section 8 of the original BLA STN 125254/0.

8.1 Trial #1 – CSLCT-FLU-04-05

8.1.1 Applicant's Protocol Number – CSLCT-FLU-04-05

"An Open-Label, Multi-Centre Study to Evaluate the Safety, Tolerability and Immunogenicity of CSL's Influenza Vaccine in a Paediatric Population (≥ 6 months to < 9 years of age)."

8.1.1.2 Objective/Rationale

- The primary objective was to evaluate the safety of CSL IVV in a pediatric population (≥ 6 months to < 3 years and ≥ 3 years to < 9 years) through the assessment of:
    - Local and systemic solicited AEs for 7 days post each vaccination;
    - Unsolicited AEs for 30 days post each vaccination;
    - SAEs for 6 months after the last primary vaccination.

- The secondary objective was to evaluate the immunogenicity of CSL IVV in a pediatric population (≥6 months to < 3 years and ≥ 3 years to < 9 years) according to the criteria of the *CPMP/BWP/214/96 Note for Guidance on Harmonization of Requirements for Influenza Vaccines.*

8.1.1.3 Design Overview

- This was a Phase III, open-label, non-randomized, non-blinded trial conducted at two sites in Australia in support of European licensure for a pediatric indication. A sample size of 300 was planned as specified by the Swedish Medical Products Agency (MPA).
- Subjects were to be assigned to Group A (150 subjects, ≥ 6 months to < 3 years) or Group B (150 subjects, ≥ 3 years to < 9 years).
- Participants were to receive 2 doses of vaccine 30 days apart (+/- 3 days): Group A 0.25 mL and Group B 0.5 mL.
- A booster dose was to be administered 12 months after the primary vaccination series.
- Day 0, Vaccination Dose 1, Visit 1: informed consent, medical history including previous influenza illness, targeted exam, pre-vaccination anti-HI antibody titers, vaccination, post-vaccination observation for 30 minutes.
- Day 0-7: 7 day Solicited AE diary card and 30 day post-vaccination Unsolicited AE diary card.
- Day 10 ± 2: review of diary cards.
- Day 30 ± 3, Vaccination Dose 2, Visit 2: return 30 day Unsolicited AE diary card, assessment of AEs, SAEs, interval history and medical evaluation, and post-vaccination anti-HI antibody titers prior to Vaccination Dose 2. 30 minute post-vaccination observation for anaphylactic reactions. Dose Two 7 and 30 day diary cards issued for solicited and unsolicited AEs respectively.
- Day 60 ± 3, Primary Vaccination Exit Evaluation: 7 and 30 day diary cards returned, all AEs and SAEs assessed, followed until resolution/stabilization. Brief medical evaluation, post-vaccination anti-HI antibody titers.
- Day 365 ± 14, Booster Vaccination: a single booster vaccination administered 12 months after Vaccination Dose 1.
- Intercurrent Flu-like Illness Visit: for symptoms occurring at any time between the first dose of Study Vaccine and the Primary Exit Evaluation. Attempt at viral isolation from a throat swab within four days of onset of symptoms.
    - Criteria for ILI: axillary temperature of ≥37.5ºC or oral temperature ≥38.0ºC, and at least one flu-like symptom (headache, cough, sore throat,

8.1.1.4 Population

- A sample size of 300 was planned
  - Group A (150 subjects, ≥ 6 months to < 3 years)
  - Group B (150 subjects, ≥ 3 years to < 9 years).

- **Inclusion Criteria**
  - Be healthy male or female children, aged ≥6 months to <9 years at the time of the first study vaccination
  - Parent(s) or Guardian(s) to provide written informed consent to participate in the study
  - Be able to provide a pre-vaccination sample of up to 5 mL of venous blood without undue distress/discomfort, and
  - Be born after a normal gestation period (between 36 and 42 weeks).

- **Exclusion Criteria**
  - Have a known allergy to eggs, chicken feathers, neomycin, polymyxin, or any components of the vaccine
  - Have had a previous influenza vaccination
  - Be experiencing clinical signs of active infection and/or an axillary temperature of ≥ 37.5°C or oral temperature of ≥ 38°C at study entry. Study entry may have been deferred for such individuals, at the discretion of the Principal Investigator
  - Have a confirmed or suspected immunosuppressive condition (including cancer), or a previously diagnosed (congenital or acquired) immunodeficiency disorder (including HIV)
  - Be currently receiving or have received (within the 90 days prior to receiving the Study Vaccine) treatment with immunosuppressive or immunomodulative medication, including systemic corticosteroids, as follows; chronic or long term corticosteroids: ≥0.5 mg/kg/day of oral prednisolone or equivalent (Note: Use of topical or inhalant corticosteroids prior to administration of the Study Vaccine or throughout the Study was acceptable)
  - Have received immunoglobulins and/or any blood products since birth or planned to have received such blood products during the study period
  - Have participated in a clinical study or use of an investigational compound (ie a new chemical or biological entity not registered for clinical use), within the 90 days prior to receiving the Study Vaccine or be planning to enter such a study during the study period
  - Be currently receiving treatment with cytotoxic drugs or treatment within the 6 months prior to administration of the Study Vaccine
  - Have a known history of Guillain-Barré Syndrome
  - Have a major congenital defect or serious illness, and

- Have a history of neurologic disorders or seizures.

8.1.1.5 Products mandated by the protocol:

- The Study Vaccine for primary vaccination contained a total of 45 µg of influenza hemagglutinin antigen per 5 mL, 15 µg of each of the three strains recommended by the Australian Influenza Vaccine Committee for the Southern Hemisphere in 2005:
  - 15µg A/New Caledonia/20/99 (IVR-116) (A/New Caledonea/20/99 (H1N1)-like)
  - 15µg A/Wellington/1/2004 (IVR-139) (A/Wellington/1/2004 (H3N2)-like)
  - 15µg B/Jiangsu/10/2003 (B/Shanghai/361/2002-like).

- The Study Vaccine to be used for the booster vaccination was to contain strains of influenza virus recommended for the Southern Hemisphere in 2006.

- Primary Vaccination Series (Days 0 and 30 ± 3):
  - Group A: 2 x 0.25mL vaccinations 30 days apart
  - Group B: 2 x 0.5mL vaccinations 30 days apart
- Booster Vaccination (Day 365 ± 14):
  - <3 years of age at time of booster: 1 x 0.25mL
  - ≥3 years of age at time of booster: 1 x 0.5mL
- Route of administration: intramuscular (IM) injection into the anterolateral aspect of the thigh for children ≤ 12 months of age; IM injection into the deltoid region of the arm for children > 12 months of age.
- The formulation was thimerosal-free and presented in a pre-filled syringe.
- Lot number: ---(b)(4)---.

8.1.1.6 Endpoints

- **Primary endpoints** were related to the safety assessment and were evaluated on all participants who received at least one dose of Study Vaccine (the Safety Population).
  - Solicited local and systemic AEs
    - Local solicited AEs included: pain, redness, and swelling
    - Systemic solicited AEs included: fever, headache, cough, sore throat, rhinitis, wheezing, myalgia, ear ache, vomiting/diarrhea, loss of appetite, and irritability
  - Unsolicited AEs
  - SAEs

- **Secondary endpoints** related to immunogenicity and were assessed on all participants who received at least one dose of the Study Vaccine consistent with the prescribed dose for their age group and who had an evaluable pre-vaccination and at least one post-vaccination anti-HI antibody titer (Evaluable Population).

Pre- and post-vaccination anti-HI antibody titers were collected and evaluated according to the *CPMP/BWP/214/96* guidance document which requires that at least one of the following criteria be met by each of the three vaccine strains:

- the proportion with a four-fold increase in HI antibody titer to a minimum of 1:40 should be > 40%;
- the mean geometric increase in HI antibody titer should by > 2.5 fold;
- the proportion of participants achieving a post-vaccination HI antibody titer of ≥ 1:40 should be > 70%.

8.1.1.7 Surveillance/Monitoring

- Please refer to the schedule of procedures from the CSR below:

Table 8 – 1 Schedule of Procedures and Assessments Study CSLCT-FLU-04-05

Assessments	Pre-Study	Day 0 Dose 1	Day 10 ± 2	Day 30 ± 3 Dose 2	Day 60 ± 3 Primary Vaccination Exit	Day 365 ± 14 Booster Dose	30 ± 3 days after Booster Vaccination Booster Vaccination Exit
Invitation to Participate	✓						
Informed Consent		✓					
Medical History (including Influenza History)		✓				✓	
Brief Medical Examination		✓		✓	✓	✓	✓
Axillary/Oral Temperature*		✓		✓		✓	
Review of Inclusion/Exclusion Criteria		✓					
Review Ongoing Eligibility				✓		✓	
Blood Sample - Immunogenicity Assessments		✓		✓	✓	✓	✓
Vaccination		✓		✓		✓	
Provision of Study Supplies and Instructions.		✓		✓		✓	
7-Day Diary Card Review		✓		✓		✓	
30-Day Diary Card Review		✓		✓		✓	
7-Day Diary Card Collection			✓		✓		✓
30-Day Diary Card Collection				✓	✓		✓
Telephone contact (if 7-Day Diary Card has not been returned)			✓				
Review of Concomitant Medications		✓		✓	✓	✓	✓
Assessment & Documentation of Adverse Events (AEs)		✓	✓	✓	✓	✓	✓
Assessment of flu-l ke Illness (including throat swabs if applicable)		✓ Participants may have attended additional visits for medical confirmation of flu-l ke symptoms at any time between Days 0 and 60 ± 3				✓ Participants may attend additional visits for medical confirmation of flu-like symptoms at any time between day 365 ± 14 and the Booster Vaccination Exit Visit.	

Assessments	Pre-Study	Day 0 Dose 1	Day 10 ± 2	Day 30 ± 3 Dose 2	Day 60 ± 3 Primary Vaccination Exit	Day 365 ± 14 Booster Dose	30 ± 3 days after Booster Vaccination Booster Vaccination Exit
Assessment & Documentation of Serious Adverse Events (SAEs)		✓ SAEs to be reviewed and documented up to 6 months after Second Primary Vaccination (Day 30 ± 3)				✓ SAEs to be reviewed and documented up to 6 months after Booster Vaccination	

Source: BLA Table II, Module 5 Vol 1 Sect 5.2.5.2 p16
* Axillary temperature was assessed in children aged less than 5 years. Oral temperature was assessed in children aged 5 years and older.

- As note in the table, subjects received a medical evaluation, post-vaccination observation, diary cards to record solicited and unsolicited AEs, telephone contact if cards were not returned, and had return visits to review AEs thirty days after both dose 1 and dose 2. SAE safety data was collected for 6 months after each dose.
- SAE was defined as any experience that:
  - Resulted in death;
  - Was life-threatening;
  - Required unexpected in-patient hospitalization or prolongation of existing hospitalization;
  - Resulted in persistent or significant disability/incapacity;
  - Was a congenital anomaly/birth defect.

- Medically significant events were defined as AEs that did not necessarily meet any of the criteria for an SAE, but that was judged by the treating physician to potentially jeopardize the patient or require medical intervention to prevent one of the outcomes defined as an SAE.
- All SAEs and medically significant events were reported and recorded regardless of assessment of attribution to the study vaccine. All SAEs were to be reported immediately to the CSL Study/Medical Monitor. An SAE form was completed and filed in both the subject's CRF and the Study Site file.
- All deaths were also reported immediately to the CSL Clinical Research Department and the Independent Ethics Committee and IRB.
- Vaccine-related and unexpected SAEs were reported to the Australian regulatory authority (Therapeutic Goods Authority) within 7 to 15 days depending on the nature of the event and according to required timeframes (similar to FDA requirements).

- Solicited AEs were graded according to the following scale:

Table 8-2 Toxicity Grading Scale for Solicited AEs - CSLCT-FLU-04-05

Symptom	Grade 0	Grade 1	Grade 2	Grade 3
Local (Vax site)				
Pain	Absent On touch	Minor rcn To touch	Cries/ Protests To touch	Cries when Moved or Spontaneously
Redness	0	<10mm	10-30mm	>30mm
Swelling	0	<10mm	10-30mm	>30mm
Systemic				
Fever (axillary)	<37.5ºC	37.5 to 38.5ºC	38.6 to 39.5ºC	>39.5ºC
Fever (oral)	<38.0ºC	39.0ºC	39.1 to 40.0ºC	>40.0ºC
Headache	none	Easily tolerated Min discomfort No interference With daily Activities	Interferes With normal Activities	Prevents Normal Activities
Cough	none	”	”	”
Sore throat	none	”	”	”
Rhinitis	none	”	”	”
Wheezing/ SOB	none	”	”	”
Myalgia	none	”	”	”
Earache	none	”	”	”
Vomiting/ Diarrhea	none	”	”	”
Loss of Appetite	none	”	”	”
Irritability	Usual behavior	More than usual, But no effect on Normal activity	Crying or Irritable more Than usual, And affects Normal activity	Cannot be Comforted

- Intensity/severity of Unsolicited AEs was graded as:
  - **Mild:** Symptoms were easily tolerated and did not interfere with daily activities
  - **Moderate:** Discomfort enough to have caused some interference with daily activities
  - **Severe:** Symptoms prevented normal every day activities.
- Relationship to the Study Vaccine was defined as follows:
  - **Not related**: In the Investigator's opinion, there was no causal relationship between the Study Vaccine and the AE

- **Unlikely:** The temporal association between the Study Vaccine and AE was such that the Study Vaccine was not likely to have any reasonable association with the AE
- **Possibly:** The AE could have been produced by the participant's clinical state or Study Vaccine
- **Probably:** The AE followed a reasonable temporal sequence from the time of Study Vaccine administration and could not be reasonably explained by the known characteristics of the patient's clinical state
- **Definitely:** The AE followed a reasonable temporal sequence from the time of Study Vaccine administration or reappeared when Study Vaccine was re-introduced.

- All AEs were recorded in the CRF. All SAEs were followed until resolution and/or stabilization.

8.1.1.8 Statistical Considerations

- The sample size of 300 was based on standards set by the Swedish Medical Products Agency specific to safety studies of influenza vaccine in pediatric populations. No inferential statistics were used. Statistical analyses for both immunogenicity and safety results comprised summary and descriptive statistics.
- Populations
  - Safety: all participants who received at least one dose of study vaccine consistent with the prescribed dose for their age group.
  - Evaluable: all participants who received at least one dose of the Study Vaccine consistent with the prescribed dose for their age group and who had an evaluable pre-vaccination and at least one post-vaccination anti-HI antibody titer; did not experience a confirmed ILI during the study; and did not meet elimination criteria.
- Immunogenicity evaluations

  The following statistics were calculated for each vaccine strain and using the results of the anti-HI antibody titers:

  - Seronegative: Number and percentage of evaluable participants with pre-vaccination serum HI titer <10 pre-vaccination.
  - Geometric mean of pre-vaccination serum HI titers and 95% confidence interval.
  - Pre-vaccination seroprotection rate: Number and percentage of evaluable participants with pre-vaccination serum HI titers ≥40, and 95% binomial confidence interval.

Reviewer comment: although the sponsor uses the definition of "seroprotection", a correlate of immune protection against influenza remains unknown and FDA does not consider this to be a measure of true "seroprotection".

- Geometric mean of post-vaccination serum HI titers and 95% confidence interval.
- Seroconversion rate: Number and percentage of evaluable participants with serum HI titer <10 pre-vaccination (undetectable) and an increase in serum HI titer to ≥40 post-vaccination.
- Significant increase: Number and percentage of evaluable participants with serum HI titer ≥10 pre-vaccination and at least a four-fold antibody titer increase post-vaccination.

- Safety evaluations
  - The number and percentage of Solicited AEs were tabulated for each age group for 7 days following Dose 1 (Day 0), Dose 2 (Day 30), and Booster vaccination (Day 365). Severity and relationship to the Study Vaccine were recorded. Those reported without a severity grading were assumed to be Grade 3 and documented in a footnote. The sponsor assumed that the first occurrence of all solicited local AEs was related to the Study Vaccine.
  - The number and percentage of Unsolicited AEs for the Primary Vaccine series was recorded for each age cohort, according to MedDRA system organ class and preferred term, severity, and causality. Unsolicited AEs were collected for 30 days following Dose 1, Dose 2, and the Booster vaccinations.
  - SAEs were reviewed and documented for up to 6 months after Dose 2 and again after the Booster vaccination.

- Changes in the Conduct of the Study or Planned Analyses

  - The protocol stated that all local AEs were to be considered related to the Study Vaccine. A change was made to the protocol such that the investigator was to determine the relationship to the Study Vaccine of local AEs which recurred after initial resolution.

  - The analysis of unsolicited AEs planned in the SAP did not consider the periods following each dose separately. Each of the planned unsolicited AE tables was generated following each dose. This change occurred after the database lock.

Reviewer comment: changes made to the planned analyses appear to be reasonable and should not have introduced bias. Please refer to the Statistical Review by Dr. Massie for additional discussion of the SAP.

8.1.2 Results of Study CSLCT-FLU-04-05 – Primary Dose

8.1.2.1 Populations enrolled and analyzed

- Study period: Initiation (date of first enrollment) March 7, 2005. Completion (last subject vaccinated) July 1, 2005. Treatment period 30 ± 3 days.

- 298 subjects were enrolled:
  - 151 Group A ≥ 6 months to < 3 years of age
  - 147 Group B ≥ 3 years to < 9 years of age

Table 8 -3 Participant Disposition Study CSLCT-FLU-04-05

	Group A ≥6mos to <3yrs		Group B ≥3yrs to <9yrs		Total	
	n	(%)	n	(%)	n	(%)
Total enrolled	151	(100)	147	(100)	298	(100)
Vaccinated Dose 1	151	(100)	147	(100)	298	(100)
Vaccinated Dose 2	148	(98.0)	145	(98.6)	293	(98.3)
Safety population (Received Dose 1)	151	(100)	147	(100)	298	(100)
Evaluable population						
Received Dose 1	143		144		287	
Received Dose 1 + 2	139		132		271	
Protocol completed	148		145		293	(98.3)
Protocol withdrawals	3	(2.0)	2	(1.4)	5	(1.7)
Reason for withdrawal						
Death	0		0		0	
SAE	0		0		0	
AE	0		0		0	
Protocol violation	0		0		0	
Withdrew consent	2	(1.3)	2	(1.4)	4	(1.3)
Moved away	0		0		0	
Lost to follow-up	1	(0.7)	0		1	(0.3)
Other	0		0		0	
Protocol violation	0		0		0	

Source: BLA Table 14.1.1, Module 5, Volume 1, Sect 5.3.5.2, Tables p2

- There were a total of 10 vaccine administration deviations reported for the 298 participants who received Dose 1, and 9 deviations for the 293 subjects who received Dose 2. Evaluation of the line listings revealed that these were primarily due to administration of vaccine in the same arm as was used for phlebotomy.

Reviewer comment: Of the 298 participants enrolled, 293 completed the study. Four withdrew consent and one was lost to follow-up. There were no withdrawals due to AEs, SAEs, or deaths. There were 19 protocol deviations in 17 participants related to vaccine

administration and 101 protocol deviations related to procedural deviations, but no subject was withdrawn from the study or excluded from the analyses because of a protocol deviation.

No protocol violations were reported by the applicant.

Table 8 - 4 Demographics and Baseline Characteristics CSLCT-FLU-04-05

Characteristic	Group A ≥6 mos to <3 years n=151	Group B ≥3 years to < 9 years n=147
Age (years)		
Mean (SD)	1.7 (0.43)	5.0 (1.73)
Median	1.9	5.0
Minimum	0.5	3.0
Maximum	2.0	8.0
Gender		
Male	74 (49.0)	66 (44.9)
Female	77 (51.0)	81 (55.1)
Prior influenza illness		
Yes	19 (12.6)	15 (10.2)
No	132 (87.4)	132(89.8)
Prior Influenza Vaccination		
Yes	0	0
No	151 (100)	147 (100)

Source: BLA Table 14.1.2, Module 5, Volume 1, Sect 5.3.5.2, Tables p3

Reviewer comment: The gender ratio was approximately equal in younger children. There were relatively more females in the older age group. No summary data was provided regarding race or ethnicity. The two study sites were located in Australia, Victoria and Western Australia. As such, a predominance of Caucasian subjects would be expected. Subjects who had previously received influenza vaccine were excluded, and only 10-12% had a history of previous influenza illness.

Concomitant Medications

- Concomitant medications listed in the Applicant's CSR tables and in the electronic datasets were evaluated. These included topical and inhaled corticosteroids which were permitted according to the protocol. Use of these agents was similar in both age groups.

General Medical History

- Frequent previous medical history included: medication and environmental allergies, eczema and other cutaneous rashes, chicken pox, impetigo, rhinitis, upper respiratory infections, asthma/wheezing, bronchiolitis, tonsillitis, gastroenteritis, and teething. Five children had a history of febrile convulsions. There were no apparent subjects with immunosuppressive conditions.

8.1.2.2 Efficacy endpoints for CSLCT-FLU-04-05 – Primary Vaccination

- The immunogenicity data for both age and dose groups is summarized in the table below:

Table 8-5 Immunogenicity Endpoints – Study CSLCT-FLU-04-05 – Primary Vaccination

Strain/ Endpoint	**FDA criteria**	**Group A ≥6mos to <3yrs**		**Group B ≥3yrs to <9yrs**	
		LB 95% CI		LB 95% CI	
	Lower bound 95% CI	Dose 1 n=143	**Dose 2 n=139**	Dose1 n=144	**Dose 2 n=132**
H1N1					
% 4-fold increase *	>40%	11.3%	**90.8%**	18.5%	**89.3%**
% with HI ≥ 1:40**	>70%	11.3%	**91.7%**	19.8%	**91.2%**
H3N2					
%4-fold increase	>40%	80.3%	**85.6%**	61.1%	**63.2%**
% with HI ≥1:40	>70%	94.7%	**97.9%**	95.7%	**97.8%**
B Strain					
% 4-fold increase	>40%	14.9%	**89.9%**	26.2%	**88.4%**
% with HI ≥ 1:40	>70%	15.5%	**91.7%**	27.5%	**90.3%**

Source: BLA Tables 14.2.1 and 14.3.1, pp10 and 12, Module 5 Vol 1 Section 5.3.5.2
*% 4-fold increase refers to the proportion of subjects with a four-fold increase in HI titer to a minimum of 1:40.
** % with HI ≥1:40 refers to the proportion with a post-vaccination HI titer of ≥1:40.

- The Evaluable Population for immunogenicity following Dose 1 excluded 8 participants in Group A and 3 participants in Group B (total 3.7%) because they did not provide both pre- and post-vaccination blood samples. Twelve participants in Group A and 15 participants in Group B (total 9.2%) of participants who received Dose 2 were excluded from the analysis for this same reason.

Reviewer comment: Following the first dose of vaccine, both age groups met the three immunogenicity endpoints for strain H3N2, unexpected success in an "unprimed" pediatric population. In contrast, but not unusual in this unprimed population, neither age group met the four-fold increase or the proportion with HI titer ≥ 1:40 endpoint for strains H1N1 and strain B after Dose 1. After 2 doses of vaccine, both age groups of children met FDA Guidance criteria for the lower bound of the 95% confidence interval for the % four-fold increase and the % with post-vaccination HI titer ≥1:40 for each of the three vaccine strains.

- Electronic datasets for study CSLCT-FLU-04-05 were not included in the original BLA submission STN 125254/0. Therefore, at the time of the original review and approval of Afluria in adults, the Reviewer evaluated the Applicant's original BLA line listings as immunogenicity result source data for study CSLCT-FLU-04-05. Line listings 16.2.8.1, 16.2.8.2, and 16.2.8.3 (Original BLA STN 125254/0 Module 5, Volume 27, Section 16.2, pp118-144) provided the listing and number of evaluable subjects in Group A and Group B for each strain. Included in these listings were subjects who were excluded from the immunogenicity analysis (summarized in Line Listing 16.2.4, Module 5 Volume 27 Section 16.2, p16), and the Reviewer, therefore, excluded these subjects from the analysis. The following table displays the results of the Reviewer's original analysis:

Table 8-6 % 4-Fold Increase (minimum HI 1:40) or Post-Vaccination HI ≥1:40 following Dose 2

Strain/ Criterion	Group A ≥6 mos to <3years n=136*	Group B ≥3 years to <9 years n=130**
H1N1		
%4-fold increase	129 (94.8%)	123 (94.6%)
% HI ≥1:40	129 (94.8%)	125 (96.2%)
H3N2		
%4-fold increase	120 (88.2%)	90 (69.2%)
% HI ≥1:40	133 (97.8%)	129 (99.2%)
B strain		
%4-fold increase	127 (93.4%)	121 (93.1%)
% HI ≥1:40	128 (94.1%)	121 (93.1%)

*derived by counting subjects in line listing and subtracting those excluded from the immunogenicity analysis. The applicant's Group A (n = 139) , Group B (n = 132).

- There were small differences between the Applicant's and Reviewer's numbers of evaluable subjects, but the overall immune response rates (point estimates) were similar to the applicant's results. Both groups of children met all three immunogenicity endpoints after two doses of vaccine.

Reviewer comment: In the current BLA PAS, STN 125254/132, the Applicant has re-submitted the same line listings (16.2.8.1 through 16.2.8.4 Module 5 Vol 3 Section 16.2) for review. In addition, the electronic datasets contain pre- and post-vaccination HI titers for both treatment groups. Please see Dr. Tammy Massie's Statistical Review for the results of the statistical analyses of the electronic source data.

The Statistical Reviewer provided analyses of immune response by gender for each age group. Please refer to Appendix 1 for these results and to Dr. Massie's review. Although the were limited and difficult to interpret because of the very small samples sizes and less than equal male:female ratio in Group B, comparable response for males and female

subjects were observed when examining the immunogenicity endpoints of seroconversion and seroprotection. Further gender specific analyses will be conducted on the post-marketing studies.

8.1.2.3 Safety Outcomes for study CSLCT-FLU-04-05 - Primary Vaccination

- All participants who received at least one dose of Study Vaccine appropriate for their age were included in the Safety Population. All 298 enrolled participants received Dose 1 and 293 participants received Dose 2. All 298 enrollees were included in the Safety Population.

- The Safety Review of study CSLCT-FLU-04-05 was based on the Applicant's tabular summaries, electronic datasets, line listings, CRFs, SAE forms and narratives.

Deaths

- There were no deaths following either Primary or Booster Vaccinations in study CSLCT-FLU-04-05. There were no discontinuations due to AEs or SAEs.

8.1.2.3.2 Serious Adverse Events – Primary Vaccination

- A total of 6 SAEs occurred during the Primary Vaccination Period (through Day 60). None were considered related to the study vaccine:
    - Three SAEs occurred within the 30-day period following Dose 1 or Dose 2: diarrhea with dehydration and fall; picornavirus viral pneumonia; and Respiratory Syncitial Virus bronchiolitis.
    - Three other unrelated SAEs were reported between 30 and 60 days following Dose 1 or Dose 2: hospitalization for type I diabetes, hospitalization for a urinary tract infection, and asthma. These SAEs are summarized in the table below and the associated CRF's will be reviewed in Section 8.1.2.3.6.
- Four additional SAEs occurred in the 6 month post-primary vaccination period (Day 60-180).
- Three more SAEs occurred in the off-study period between end of the 6-month post-Primary follow-up period and the start of the Booster series.
- Materials reviewed included the Applicant's summary report (Module 5, Vol 1,5.3.5.2, CSR pp74-75), case narratives (Mod 5, Vol 1, CSR section 16.1.13), CRFs and SAE report forms (Mod 5, Vol 5, Sect 5.3.7), Overview of Safety (Mod 2, vol 1, Sect 2.7.4), and electronic datasets (include only those SAEs that occurred in the 30 days following each vaccination).

Table 8-7 Serious Adverse Events following Primary Dose 1 and Dose 2 through Day 180 - CSLCT-FLU-04-05

Pt ID/ Group	SAE	Asso'd Dose	Time To onset	Grade	Tx	outcome	Rel
013/A	RSV bronchiolitis	2	18d	Severe	hosp	Resolved	No
124/A	Dehydration due to diarrhea	2	6	Severe	hosp	Resolved	No
087/B	Picornavirus Pneumonia	1	0	Severe	MD	Resolved	No
106/A	UTI	2	35	Severe	Hosp	Resolved	No
063/B	Type 1 diabetes	2	38	Severe	Hosp	Ongoing	No
111/A	Asthma	2	37	-	Hosp	-	No
006/A	Meningococcal sepsis	2	94	Severe	Hosp	-	No
089/B	Autism spectrum Disorder	2	>90	-	Med signif	Sx preceded Vax	No
147/A	Laceration to mouth	2	87	-	Hosp	-	No
022/A	Rotavirus gastroenteritis	2	41	-	Hosp	-	No
Off Study Period – between end of 6 month follow-up and 1 year Booster Dose							
085/A	Exacerbation of asthma	2	>180	-	Hosp	-	No
088/B	Exacerbation of asthma	2	>180	-	Hosp	-	No
105/B	Asthma	2	>180	-	Hosp	-	

8.1.2.3.3 Solicited Adverse Events – Primary Vaccination

- Solicited Local (injection site) and Systemic AEs according to dose and age/treatment group are summarized in the following two tables, based on the Applicant's Tables VI, VII, VIII, and IX, Module 5, Vol 1, Section 5.3.5.2, CSR pp59-60 and 64-65:

Table 8-8 Solicited AEs by Severity Grade – CSLCT-FLU-04-05 (Dose 1)

	Group A, n=151 ≥6 mos to <3 years				**Group B, n=147 ≥3 years to <9 years**			
Event	Grade 1 (%)*	Grade 2 (%)	Grade 3 (%)	**Total**	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	**Total**
Local AEs								
Pain	29.8	5.3	1.3	36.4	46.3	10.9	2.0	59.2
Redness	26.5	8.6	0.7	35.8	26.5	9.5	0.7	36.7
Swelling	10.6	4.6	0.7	15.9	16.3	6.8	1.4	24.5
Systemic AEs								
Fever	19.9	2.6	0	22.5	11.6	2.7	1.4	15.6
Headache	2.0	0	0	2.0	8.2	3.4	2.0	13.6
Cough	19.9	1.3	0	21.2	15.0	3.4	0.7	19.0
Sore throat	1.4	0.7	0	2.0	6.8	0.7	0.7	8.2
Rhinitis	35.8	1.3	0	37.1	19.7	1.4	0	21.1
Wheezing	2.6	0.7	0	3.3	2.7	0	0	2.7
Myalgia	0.7	0	0	0.7	9.5	2.7	1.4	13.6
Ear ache	2.7	0.7	0	3.3	4.1	0	0	4.1
Vomiting/ Diarrhea	12.6	1.3	0.7	14.6	3.4	2.0	2.0	7.5
Loss of Appetite	15.2	3.3	0.7	19.2	4.8	2.0	0.7	7.5
Irritability	32.5	13.9	1.3	47.7	13.6	6.1	0.7	20.4

*For any given AE, the denominator for the % is the # of subjects in the Safety Population minus the # of subjects who were not assessed for that AE.

Table 8-9 Solicited AEs by Severity Grade – CSLCT-FLU-04-05 (Dose 2)

	Group A n=151 ≥6 mos to < 3 years				Group B n=147 ≥3 years to <9 years			
Event	Grade 1 %*	Grade 2 %	Grade 3 %	Total	Grade 1 %	Grade 2 %	Grade 3 %	Total
Local AEs								
Pain	25.2	11.9	0	37.1	42.2	17.7	2.0	61.9
Redness	31.1	6.6	0	37.7	26.5	12.2	6.8	45.6
Swelling	17.2	3.3	0	20.5	17.0	8.2	2.0	27.2
Systemic AEs								

	Group A n=151 ≥6 mos to < 3 years				Group B n=147 ≥3 years to <9 years			
Fever	15.2	6.6	0.7	22.5	7.5	0.7	0	8.2
Headache	2.0	0.7	0.7	3.3	8.8	1.4	0.7	10.9
Cough	23.8	6.6	1.3	31.8	17.7	1.4	0.7	19.0
Sore throat	2.7	1.3	1.3	5.3	8.2	2.0	0.7	10.9
Rhinitis	37.1	9.3	1.3	47.7	25.9	2.7	0	28.6
Wheezing	6.6	2.0	0	8.6	1.4	0.7	0	2.0
Myalgia	2.0	0.7	0	2.7	6.1	2.0	0	8.2
Earache	2.0	1.3	0	3.4	0.7	0.7	0	1.4
Vomiting/ Diarrhea	9.3	2.0	2.6	13.9	6.1	0.7	0	6.8
Loss of Appetite	15.9	5.3	2.6	23.8	4.8	0.7	0	5.4
Irritability	24.5	11.9	4.6	41.1	15.0	2.0	0	17.0

*For any given AE, the denominator for the % is the # of subjects in the Safety Population minus the # of subjects who were not assessed for that AE.

- The following table summarizes all Solicited AEs associated with each dose in both age/treatment groups:

Table 8-10 Summary of Solicited AEs CSLCT-FLU-04-05

	Group A, n=151 ≥6 mos to <3 years		**Group B, n=147 ≥3 years to <9 years**	
Event	Dose 1	Dose 2	Dose 1	Dose 2
Local AEs	55.0	53.6	70.1	70.1
Pain	36.4	37.1	59.2	61.9
Erythema	35.8	37.7	36.7	45.6
Swelling	15.9	20.5	24.5	27.2
Systemic AEs	76.2	70.7	57.1	55.1
Irritability	47.7	41.1	20.4	17.0
Rhinitis	37.1	47.7	21.1	28.6
Fever	22.5	22.5	15.6	8.2
Cough	21.2	31.8	19.0	19.0
Loss of appetite	19.2	23.8	7.5	5.4
Vomiting/diarrhea	14.6	13.9	7.5	6.8

	Group A, n=151 ≥6 mos to <3 years		Group B, n=147 ≥3 years to <9 years	
Headache	2.0	3.3	13.6	10.9
Myalgia	0.7	2.7	13.6	8.2
Sore throat	2.0	5.3	8.2	10.9
Wheezing/shortness of breath	3.3	**8.6**	2.7	2.0
Earache	3.3	3.4	4.1	1.4

- The data presented in this review include all Solicited AEs irrespective of the assessment of relatedness.
- If an AE was reported more than once for a given subject, the maximum severity grade was used for the analysis. For the few cases where the severity grade was not known, the maximum severity Grade 3 was assigned.
- Oral and axillary fever measurements were combined in the report.

Reviewer Comment: According to the sponsor's data, pain, headache, sore throat, myalgia and earache may not have been assessed in all participants (at most three) in Group A, resulting in slightly different denominators and percentages. For any given AE, the denominator for the percentages is the number of subjects in the Safety Population minus the number of subjects who were not assessed for that AE. All subjects in Group B were assessed for each parameter.

Group A (6 months to < 3 years)

- There were no Serious Solicited AEs
- For the younger age Group A, the overall frequency of local and systemic solicited AEs after Dose 1 compared to Dose 2 was similar. Overall, 54-55% of subjects experienced local symptoms and 70-76% experienced systemic symptoms. Injection site pain and erythema, irritability, rhinitis, fever, and cough were the most frequently reported events. Fever occurred in 23% of children following both doses, and 1 episode was severe. Most reactogenicity events were mild to moderate. There were very few severe (Grade 3) reactions, and these included events where parents did not report severity such that a Grade 3 was assigned. The majority of events were considered vaccine-related by the investigator.

Group B (3 to <9 years of age)

- There were no Serious Solicited AEs.
- Overall, 70% of children in Group B reported local injection site symptoms and 55-57% reported systemic symptoms after either dose of study vaccine. The frequency of events following Dose 1 and Dose 2 were similar. The most frequent local symptoms were injection site pain, erythema and swelling. The most frequent systemic symptoms were irritability, rhinitis, cough, headache and myalgia. Fever was reported by 16% after Dose 1 and by 8% after Dose 2.

- Most events were mild to moderate in severity. The majority of events were considered vaccine-related.
- Children in Group B reported more local reactogenicity and more headache, myalgia and sore throat relative to the younger children, but experienced less fever, irritability, rhinitis, cough, anorexia, vomiting and diarrhea.

Reviewer comment: In general, solicited adverse events were consistent with previous descriptions of reactogenicity events for influenza vaccines. Local symptoms were more common than systemic events, and, as expected in immunologically naïve individuals, the overall reactogenicity was greater than that reported for adults.

Reviewer comment: Source data from Line Listings 16.2.9.1 and 16.2.9.2 Module 5 Volume 27 Section 16.2 pp155-211 from the original BLA STN 125254/0 were reviewed. For each solicited AE, the number of subjects and severity grade was almost identical to the applicant's summaries displayed in the above tables. The electronic datasets submitted with STN 125254/132 were evaluated for all Grade 3 Solicited AEs and SAEs. The reviewer's findings were identical to the Applicant's report.

- Wheezing and shortness of breath occurred with disproportionately greater frequency after Dose 2 in Group A relative to Dose 1 and to both doses in Group B participants. Among younger children in Group A, this event occurred in 13 (8.6%) of subjects after Dose 2 compared to a rate of 3.3% after Dose 1 and 3.9% after the Booster Dose one year later. The older children in Group B experienced lower frequencies of wheezing/shortness of breath overall: 2.7% after Dose 1, 2.0% after Dose 2, and 4.6% after the Booster Dose one year later.

  Results identical to the Applicant's report were found by evaluating the electronic datasets and are displayed in the table below:

Table 8-11 Solicited Wheezing/Shortness of Breath in the 7 Days following Vaccination – Both Age Groups, Primary and Booster Doses

Group A % (n) 6 months to < 3 years			Group B % (n) 3 to < 9 years		
Dose 1 N=151	Dose 2 N=151	Booster N=76	Dose 1 N=147	Dose 2 N=147	Booster N=196
3.3 (5)	**8.6 (13)**	3.9 (3)	2.7 (4)	2.0 (3)	4.6 (9)

Source: Mod 2 Vol 1 Sect 2.7.4 p14. Identical results found by evaluation of the electronic datasets.

Table 8-12 Summary of all Wheezing/Shortness of Breath Solicited AEs Following Primary or Booster Vaccination – CSLCT-FLU-04-05

Pt ID	Dose	Gp (age)	Max grade	SAE	Day onset	Duration (days)	Tx	resolved	related	Med Hx
1013	P2	A 1.1	2	N	1	5	N	Y	poss	bronchiolitis
1018	P1	A 2	1	N	1	6	N	Y	prob	Eczema,URI
1018	P2	A 2	1	N	1	7	N	Y	prob	Eczema,URI
1018	B	B 3	2	N	3	4	N	Y	poss	Eczema,URI
1025	P1	A 2	1	N	1	5	N	Y	prob	wheezing
1025	P2	A 2	1	N	0	7	N	Y	prob	wheezing
1025	B	B 3	1	N	1	1	N	Y	prob	wheezing
1053	P1	A 2	1	N	4	2	N	Y	def	tonsillitis
1054	P2	A 0.9	1	N	5	2	N	Y	def	Otitis media
1059	P1	A 1.75	1	N	6	Ongoing	N	no	prob	asthma
1066	B	A 1	3	N	0	1	N	Y	def	-
1067	B	B 3	2	N	0	1	N	Y	def	-
1084	P2	A 1.6	1	N	5	2	N	Y	def	asthma
1085	P2	A 2	1	N	3	4	N	Y	def	asthma
1098	P2	A 2	1	N	3	2	N	Y	def	eczema
1100	P1	A 1.8	1	N	3	1	N	Y	def	asthma,URI
1106	P2	A 1.8	1	N	3	4	MD	Y	def	URI
1114	P2	A 2	1	N	1	3	N	Y		asthma
1116	B	A 1	1	N	4	1	N	Y	def	-
1129	P2	A 2	1	N	4	3	N	Y	def	-
1133	P2	A 2	2	N	5	2	N	Y	prob	otitis
1134	B	A 2	1	N	1	3	N	Y	No	wheezing
1137	B	B 3	2	N	5	2	ER	ongoing	poss	constipation
1138	P2	A 1.8	1	N	3	1	N	Y	def	URI
1152	P2	A 2	1	N	0	4	N	Y	No	asthma
1163	P1	A 2	2	N	1	2	N	Y	def	asthma
1163	B	B 3	1	N	1	5	N	Y	poss	asthma
1236	P2	A 2	1	N	1	3	N	Y	def	asthma
2014	P2	B 8	2	N	0	7	N	Y	prob	asthma
2014	B	B 9	1	N	0	2	N	Y	poss	asthma
2023	B	B 9	1	N	0	1	N	Y	Def	asthma

Pt ID	Dose	Gp (age)	Max grade	SAE	Day onset	Duration (days)	Tx	resolved	related	Med Hx
2028	P2	B 5	1	N	6	?	N	ongoing	No	asthma
2035	P1	B 6	1	N	6	?	N	Y	prob	asthma
2057	B	B 6	2	N	1	2	MD	Y	Def	
2066	P1	B 6	1	N	0	7	MD	ongoing	No	asthma
2066	P2	B 6	1	N	0	7	N	Y	No	asthma
2078	P1	B 3	1	N	1	1	N	Y	def	asthma
2085	P1	B 5	1	N	5	2	N	Y	prob	-
2138	B	B 6	2	N	1	1	MD	Y	def	-

Age = age in years at time of dose and wheezing

P=primary; B=booster

MD=saw medical doctor; ER= emergency room visit

Reviewer Comment: There were a total of 32 cases of wheezing/shortness of breath in the 7 days following vaccinations with either the primary or booster doses. Most were considered mild, none were SAEs, and only 5 prompted a visit to a healthcare provider. Most of these children had a past medical history that included asthma, wheezing or bronchiolitis. The disproportionate number of cases (8.6%) in Group A following Dose 2 appears to be a statistical "blip" rather than a trend. Wheezing and bronchiolitis is common in young children, and there is no biological reason (other than an anaphylactic reaction) for an inactivated influenza vaccine to cause wheezing or shortness of breath. An imbalance of wheezing and shortness of breath has not been noted in the adult studies submitted to the original Afluria BLA.

There is no placebo group for CSLCT-FLU-04-05 for comparison, but data from clinical trials in children are summarized in the Package Inserts for FluMist and Fluzone: Wheezing occurred in 5.9% of FluMist recipients 6 to 23 months; in 2.1% of FluMist recipients 24 to 59 months; in 3.8% of Fluzone recipients 6 to 23 months; and in 2.5% of Fluzone recipients 24 to 59 months. The results of the Solicited AEs including wheezing/shortness of breath will be reported in Section 6.2 of the Afluria label.

8.1.2.3.4 Unsolicited Adverse Events – Primary Vaccination

Unsolicited AEs were collected for 30 days following Dose 1 and for 30 days following Dose 2. The following table is based on the applicant's Table 14.4.2.1, Mod 5, Vol 1, section 5.3.5.2, p 17:

Table 8-13 Unsolicited AEs by Number of Events Occurring within 30 Days of Receiving Dose 1 or Dose 2 – CSLCT-FLU-04-05

Parameter	All Participants n, (%)	Group A ≥6 mos to <3 years n, (%)	Group B ≥3 years to <9 years n, (%)
Number of AEs	658 (100)	388 (100)	270 (100)
Serious	4 (0.6)	3 (0.8)	1 (0.4)
Non-serious	654 (99.4)	385 (99.2)	269 (99.6)
Vaccine-related	76 (11.6)	41 (10.6)	35 (13.0)
Non-related	582 (88.4)	347 (89.4)	235 (87.0)
Severity			
Mild	309 (47.0)	172 (44.3)	137 (50.7)
Moderate	273 (41.5)	175 (45.1)	98 (36.3)
Severe	76 (11.6)	41 (10.6)	35 (13.0)

The following table presents a summary of the total number of subjects who experienced at least one Unsolicited AE following either Dose 1 or Dose 2 of the primary series according to age group, and is based on the Applicant's Table 14.4.3.1, Module 5, Volume 1 Section 5.3.5.2, p.19:

Table 8-14 Number of Subjects with at least One Unsolicited AE following either Dose 1 or Dose 2 of the Primary Series – CSLCT-FLU-04-05

Characteristic	All Participants (N=298) n, (%)	Group A ≥6 mos to <3 years (n=151) n, (%)	Group B ≥3 years to <9 years (n=147) n, (%)
# with at least one AE	240 (85.5)	133 (88.1)	107 (72.8)
Serious	3 (1.0)	2 (1.3)	1 (0.7)
Related SAE	0	0	0
# with Vaccine-related AE	55 (18.5)	29 (19.2)	26 (17.7)
# with AE by Severity			
Mild	163 (54.7)	90 (59.6)	73 (49.7)
Moderate	150 (50.3)	92 (60.9)	58 (39.5)
Severe	45 (15.1)	23 (15.2)	22 (15.0)
#Discontinued due to AE	0	0	0
#Discontinued due to SAE	0	0	0
#Deaths	0	0	0

- The majority of events were considered non-serious and unrelated to the Study Vaccine. According to the applicant's summary, a total of 658 unsolicited AEs were reported by 240 participants: 388 events in 133 Group A participants and 270 events in 107 Group B participants. 11.6% of all AEs were assessed as severe, 41.5% as moderate, and 47% as mild. 11.6% of all AEs were assessed as possibly, probably or definitely related to the Study Vaccine.
- Three SAEs occurred during the Primary vaccination period (within the 30-day period following Dose 1 or Dose 2): diarrhea with dehydration and fall; viral pneumonia; and Respiratory Syncitial Virus Bronchiolitis. None of these were considered vaccine-related. CRFs and case narratives were requested for all SAEs and will be reviewed in the SAE section to follow.
- As noted in Sections 8.1.2.3.1 and 8.1.2.3.2, there were no deaths following primary or booster vaccinations in this study, and there were no discontinuations due to AEs or SAEs. SAEs have been summarized in Section 8.1.2.3.2, and further details of the associated CRFs, SAE forms and narratives are presented in Section 8.1.2.3.6

The following summary table is based on the Reviewer's evaluation of the electronic datasets submitted September 10, 2009:

Table 8-15 Summary of Unsolicited AEs – CSLCT-FLU-04-05 – Primary Vaccination - Safety Population – Reviewer Evaluation of Electronic Datasets

	All subjects N=298		Group A N=151		Group B N=147	
Parameter	N(%)	E	N(%)	E	N(%)	E
All Unsolicited AEs	240 (80.5)	658	133 (88.1)	388	107 (72.8)	270
Mild	163 (54.7)	309	90 (59.6)	172	73 (49.7)	137
Moderate	150 (50.3)	273	92 (60.9)	175	58 (39.5)	98
Severe	45 (15.1)	76	23 (15.2)	41	22 (15.0)	35
SAE	3 (1.0)	4	2 (1.3)	3	1 (0.7)	1
Mild	0	0	0	0	0	0
Moderate	2 (0.7)	3	1 (0.7)	2	1 (0.7)	1
Severe	1 (0.3)	1	1 (0.7)	1	0	0
Discontinued b/o AE	0	0	0	0	0	0
Discontinued b/o SAE	0	0	0	0	0	0
Deaths	0	0	0	0	0	0

Reviewer comment: Results from the Reviewer's evaluation of the electronic datasets were identical to the Applicant's report.

- The following table summarizes Unsolicited AEs that occurred with a frequency of ≥ 5%:

Table 8-16 Unsolicited AEs Occurring with a Frequency of ≥ 5% within 30 Days of Receiving Dose 1 or Dose 2 in the Pediatric Population CSLCT-FLU-04-05

Organ System/ Preferred term	**All Participants (n=298) %***	**Group A ≥6 mos to 3 years (n=151) %**	**Group B ≥3 years to <9 years (n=147) %**
Gastrointestinal disorders	23.2	31.8	14.3
Teething	9.1	17.9	0.0
Vomiting	6.4	7.9	4.8
General/administration site conditions	25.2	31.8	18.4
Influenza-like illness	15.8	21.9	9.5
Pyrexia	9.4	11.9	6.8
Infections and infestations	48.7	56.3	40.8
Nasopharyngitis	10.7	11.9	9.5
Rhinitis	18.5	19.9	17.0
Upper resp infection	13.1	15.2	10.9
Injury, poisoning, and procedural complications	5.0	6.0	4.1
Musculoskeletal/connective tissue disorders	3.0	0.7	5.4
Nervous system disorders	6.0	3.3	8.8
Headache	4.7	2.0	7.5
Psychiatric disorders	6.4	9.9	2.7
Irritability	4.7	7.9	1.4
Respiratory, thoracic, and mediastinal disorders	34.2	35.1	33.3
Cough	23.2	23.8	22.4
Pharyngolaryngeal pain	3.4	0.7	6.1
Rhinorrhea	11.4	12.6	10.2

The following table is based on the applicant's Table 14.4.4.1, Mod 5, Volume 1, Section 5.3.5.2, p 21.

*% based on the number of subjects experiencing the AE in the respective group

- The most frequent unsolicited AEs in the younger age Group A by preferred term were teething (17.9%), influenza-like illness (21.9%), rhinitis (19.9%), URI (15.2%), and cough (23.8%).
- The most frequent AEs by preferred term in the older age Group B were rhinitis (17.0%), cough (22.4%), ILI (9.5%), nasopharyngitis (9.5%), and rhinorrhea (10.2%).
- Severe Unsolicited AEs occurring within 30 days of either Primary Dose 1 or Dose 2 (Table 8-16):

Table 8-17 Summary of all Severe Unsolicited AEs Occurring within 30 Days of either primary Dose 1 or Dose 2 – CSLCT-FLU-04-05

	#Subjects with Severe Unsolicited AEs	
System Organ Class Preferred term	Group A (N=151) n	Group B (n=147) n
Ear and labyrinth ds		
Ear pain	1	1
Gastrointestinal ds		
Abdominal pain	0	2
Abdominal pain upper	0	1
Mouth ulceration	0	1
Nausea	1	0
Oral pain	1	0
Vomiting	2	**4**
General and Admin Site Ds		
Fatigue	0	0
ILI	**7**	**6**
Pyrexia	**5**	1
Infections and infestations		
Bronchiolitis	1	0
Bronchitis	1	0
Croup infectious	0	1
Ear infection	1	0
LRI	2	0
Nasopharyngitis	2	1
Otitis media	1	1

	#Subjects with Severe Unsolicited AEs	
System Organ Class Preferred term	Group A (N=151) n	Group B (n=147) n
Pharyngitis	1	0
Rhinitis	0	2
Sinusitis	1	0
Tonsillitis	2	1
URI	3	1
Viral infection	0	1
Injury, poisoning, procedures		
Laceration	1	0
Toe crushing	1	0
Upper limb fracture	0	1
Musculoskeletal and Connective Tissue Ds		
Muscle cramp	0	1
Myalgia	0	1
Nervous System ds		
Febrile convulsion	0	1
Headache	0	1
Lethargy	0	1
Psychiatric disorders		
Irritability	1	0
Respiratory, thoracic, mediastinal ds		
Asthma	1	0
Cough	2	2
Stridor	1	0

Source: Applicant's electronic datasets submitted to STN 125254/132 on 9/10/09.

Reviewer comment: For each type of Severe Unsolicited AE, there were relatively few subjects who experienced any single event. The exceptions were: ILI (7 in Group A and 6 in Group B); pyrexia (5 in Group A); and vomiting (4 in Group B). Of these three relatively more frequent Severe Unsolicited AEs, those that occurred less than 7 days after the study vaccination were: ILI (3 in Group A and 3 in Group B) and pyrexia (1 in Group A).

- Severe Unsolicited AEs Assessed as Vaccine-Related

  Of 76 reported Severe Unsolicited AEs, 13 events in 10 subjects (3.4% of all 298 primary vaccine recipients) were assessed as related to the study vaccine. These reactions were primarily pyrexia and ILI (Table 8-17):

Table 8-18 All Severe Unsolicited AEs Assessed as Vaccine-Related

Study CSLCT-FLU-04-05

Group Subject	Severe AE	Dose	Time to Onset (Days)	SAE? Y/N	Tx? Y/N	Assessment
Group A						
1126/A	ILI	1	4	N	N	Definitely
	Pyrexia (5/12/05)	2	2	N	N	Definitely
	Pyrexia (5/14/05)	2	4	N	N	Definitely
1127/A	Irritability	2	1	N	N	Definitely
1151/A	ILI	1	2	N	MD	Definitely
Group B						
2051/B	ILI	1	1	N	N	Definitely
2057/B	ILI	1	0	N	HCW	Definitely
2085/B	ILI	1	6	N	N	Probably
2088/B	Abdominal pain	1	2	N	N	Definitely
2095/B	Pyrexia	2	7	N	N	Probably
	Vomiting	2	7	N	N	Probably
2109/B	Tonsillitis	2	7	N	MD	Possibly
2126/B	Fatigue	1	0	N	N	Definitely

Source: Applicant's electronic datasets and line listings

*ILI = influenza-like illness; MD=saw medical doctor; saw healthcare professional

- Throat swabs for ILI
  - Throat swabs for influenza culture were collected on subjects who met criteria for an intercurrent ILI between Dose 1 and Dose 2 and between Dose 2 and Day 60 Exit Primary Evaluation. 12 specimens were collected from subjects in Group A and 5 from subjects in Group B. All tested negative for influenza.

Reviewer Comment: Although attribution is uncertain, ILI and pyrexia will be described in Section 6.2 of the label as being among the more common adverse events following vaccination.

8.1.2.3.5 Adverse Events of Significant Interest (AESIs) – Primary and Booster Dose Data

- The datasets and Applicant's summary tables were examined further for events of special interest following both primary and booster doses. Of particular interest were hypersensitivity, neurologic or autoimmune type events. The datasets were searched for terms that included immune system disorders, hypersensitivity, drug hypersensitivity, adverse drug reaction, allergy, anaphylaxis, hives, urticaria, serum sickness, vasculitis, swelling, angioedema, allergic asthma, anemia, lymphadenopathy, thrombocytopenia, immune thrombocytopenia, arthralgia, myalgia, synovitis, rash, rash pruritic, conjunctivitis (for cases suggestive of oculorespiratory syndrome). The datasets were also searched for neurologic disorders using terms that included acute disseminated encephalomyelitis, Guillain Barre Syndrome, myelitis, neuritis, and paraesthesia.

Table 8-19 Adverse Events of Special Interest following Primary or Booster Vaccination – CSLCT-FLU-04-05

Adverse Event (Preferred Term)	**# cases**	**Pt ID**	**Gp**	**Dose**	**Onset (d)**	**SAE**	**Grade**	**Causality/ Comments**
Lymphadenopathy	1	2074	B	2	31	N	mild	N
Conjunctivitis	6	-	-	-	-	-	-	None suggestive of oculorespiratory Syndrome
Mouth ulceration	3	1065 1078 2018	A A B	2 2 1	9 11 27	N N N	Mod Sev Mild	N N N
Hypersensitivity	1	1028	A	2	14	N	Mild	N/allergic rcn
Arthralgia (shoulder)	1	2010	B	1	0,6	N	Mild	Y
Febrile convulsion	1	2024	B	2	30	N	Severe	N/no problem with booster.
Asthma	6	1008	A	1	24	N	Mild	N/saw HCW
		1033	A	2	15	N	Mild	N/saw MD
		1130	A	1	27	N	Severe	N/saw MD
		1137	A	B	19, 27	N	Severe	N/saw MD
		1163	A	2	16,26	N	Mod	N
		2109	B	1	27	N	Mild	N/saw MD
Dyspnea	1	1095	B	B	12	N	Mod	N
Stridor	1	1045	A	2	15	N	Severe	N/saw MD
Wheezing	3	1084	A	2	9	N	Mild	N
		1137	B	B	7	N	Severe	Possibly/ER
		1152	A	1	25	N	Mild	N
Rash	5	1019	A	1	6	N	Mild	N
		1025	A	1	5	N	Mild	N

Adverse Event (Preferred Term)	**# cases**	**Pt ID**	**Gp**	**Dose**	**Onset (d)**	**SAE**	**Grade**	**Causality/ Comments**
		1096	A	1	26	N	Mild	N/saw MD
		2036	B	1	20	N	Mild	N
		2096	B	B	26	N	Mod	N
Rash generalized	1	2051	B	2	25	N	Mod	N/saw MD
Urticaria	1	2104	B	2	0	N	Mild	Definitely

Dose B=booster, Causality N=not related

Reviewer Comment: Search of the datasets for AESI did not reveal unusual or unexpected cases of vaccine-associated hypersensitivity, neurologic or autoimmune disorders.

8.1.2.3.6 SAE Case Report Forms Reviewed – Primary Vaccination

- The applicant was asked to provide the CRFs for the pediatric SAEs on July 30, 2007. A response was received on August 9, 2007 in Amendment 125254/0.11 to the original BLA STN 125254/0. The following SAE summaries are based on those original CRFs and, in addition, on materials provided with the pediatric BLA Supplement STN 125254/132, including: the Applicant's summary report (Module 5, Vol 1,5.3.5.2, CSR pp74-75); case narratives (Mod 5, Vol 1, CSR section 16.1.13); CRFs and SAE report forms (Mod 5, Vol 5, Sect 5.3.7); Overview of Safety (Mod 2, vol 1, Sect 2.7.4); and electronic datasets (e-datasets include only those SAEs that occurred in the 30 days following each vaccination).

- Subject A124: Severe dehydration and severe diarrhea. 6 month old female vaccinated April 12, 2005. Previous history of GERD and eczema. Onset of grade 3 diarrhea and dehydration on May 18, 2007, required hospitalization, judged an SAE, but not related to the study vaccine. Child's brother had had diarrheal illness 1 week prior to the subject onset. Resolved by May 23, 2007.
- Subject B087: 3 year old female vaccinated April 5, 2005. Rhinitis began on April 8th, fever, headache, cough, vomiting on April 9th. Saw GP, treated for ILI with antibiotics, throat swab revealed picornavirus, negative for influenza. CXR revealed RLL pneumonia, diagnosed as viral pneumonia. Judged not vaccine-related. Resolved June 2, 2005.
- Subject A013: 13 month old female vaccinated April 22, 2005. Hospitalized June 12, 2005 with RSV bronchiolitis. Resolved June 25, 2005. Judged not vaccine-related.
- Subject A106: 2 year old female vaccinated April 7, 2005 and May 5, 2005. June 9th, 35 days post-dose 2, lethargic. Hospitalized June 13 to June 16, 2005 with E.coli UTI, structural abnormalities with reflux on renal ultrasound. Resolved with antibiotic therapy, planned elective surgery. Withdrew from study March 22, 2006. Judged not vaccine-related.

- Subject B063: 6 year old male vaccinated April 5, 2005 and May 10, 2005. Onset polyuria, polydipsia June 17, 2005, 38 days after dose 2. Hospitalized June 27, 2005 with new onset Type I diabetes mellitus. Discharged June 28, 2005. Judged not vaccine-related.
- Subject A111: Dose 1 on April 11, 2005, Dose 2 May 20, 2005. Hospitalized with asthma June 26, 2005. Assessed as not related.
- Subject A006: Dose 1 on April 6, 2005, Dose 2 May 6, 2005. Hospitalized with meningococcal sepsis on August 8, 2005. Stabilized and discharged. Not related.
- Subject B089: Age 4, Dose 1 on April 6, 2005, Dose 2 on May 6, 2005. Mother had noted behavioral problems since the age of 2, becoming more pronounced in 2005. Diagnosed with autism spectrum disorder in August 2005. Ongoing at end of study. Assessed as a Medically Significant event, but not related to the study vaccine.
- Subject A147: Dose 1 on April 28, 2005 and Dose 2 on May 30, 2005. One day hospitalization on August 25, 2005 for laceration to the roof of the mouth. Assessed as Medically Significant but not related to the study vaccine.
- Subject A022: Dose 1 on April 28, 2005, Dose 2 on May 26, 2005. Hosptialized on July 6, 2005 with fever, vomiting, and dehydration due to rotavirus gastroenteritis. Resolved. Assessed as not related to study vaccine.
- In addition, there were 3 cases of asthma/exacerbation of asthma (A085, B088, B105) that occurred more that 180 days after Dose 2 and before the booster dose of vaccine. Assessed as not related.

Reviewer comment: The Reviewer agrees with the Applicant's assessment that there do not appear to be any safety signals or SAEs caused by the study vaccine.

8.1.2.3.7 Influenza-like illness: Overall, 47 participants experienced episodes of ILI. All throat swabs tested were negative for influenza virus.

8.1.3 CSLCT-FLU-04-05 – Booster Vaccination Study Summary and Results

8.1.3.1 Overview

- Product: inactivated trivalent influenza vaccine with 15mcg of HA for each of the three antigens H1N1, H3N2, and B strain (as for the primary vaccination series).
- Sites: same as for the primary series
- Study Period: Days 365 (+/-14) to 395 (+/-3) after the initial primary vaccination.
  Active study period: 30 +/-3 days.
  Date of first Booster vaccination: February 27, 2006.
  Date last subject completed: June 12, 2006.
- Objectives: as for the primary series. SAEs followed for 6 months post-booster vaccination.
- Design: Phase 3, multicenter, open-label. Approximately 12 months after receiving the first dose of study vaccine, participants returned to the study sites

- Populations for Analysis
    - Safety: all participants who received the Booster Dose as prescribed for their age group.
    - Immunogenicity: all participants who received the correct Booster Dose, had pre- and post-vaccination titers, and who did not have a laboratory-confirmed ILI.
- HI assays and criteria for immune responses were the same as for the Primary Vaccine phase of the study.

8.1.3.2 Results

8.1.3.2.1 Populations enrolled and analyzed

Table 8-20 Subject Disposition – CSLCT-FLU-04-05 - Booster

	Group A 6mos to <3 years	**Group B 3 to <9 years**	**Total**
Total enrolled	76	197	273
Vaccinated	76	197	273
Completed	74	192	266
Withdrawn from all Analyses (incorrect dose)		1	1
Withdrawn	2	5	7
Withdrew consent	1	3	4
Lost to follow-up	0	2	2
Unable to attend	1	0	1
Adverse event	0	0	0
SAE	0	0	0
Protocol violation	0	0	0
Safety Population	76	196	272
Evaluable Population	61	174	235

Source: Table 14.1.1A Mod5, Vol 2, Sect16.4, Tables p 2

Reviewer comment: There were few withdrawals from the study, and none due to AEs or SAEs.

Table 8-21 Demographics – Booster Population

	Group A 6mos to <3 years N=76	**Group B 3 to <9 years N=197**	**Total N=273**
Age (years)			
Mean	1.8	5.1	4.2
Gender			
Male	32	98	130
female	44	99	143

Source: Table 14.1.2A Mod 5,Vol 2,Sect16.4, Tables p3

Reviewer comment: The mean age for subjects in Group A was 1.8 years and for Group B was 4.2 years of age. Overall, there were approximately as many male as female participants.

8.1.3.2.2 Immunogenicity Results – Booster Vaccination

- Exclusions from the Evaluable Population
  - Group A: due to withdrawal (2), protocol deviations (13)
  - Group B: due to withdrawal (5), protocol deviations (16), ILI (2)

- Seroconversion/Significant Increase and Proportion of Subjects with Post-Vaccination HI Titers ≥ 1:40

Table 8-23 Immunogenicity Endpoints – CSLCT-FLU-04-05 – Booster Vaccination

Antigen/ Endpoint (LB 95% CI)	Group A N=61	Group B N=174
H1N1		
%4-fold rise	85.6	66.3
% HI ≥ 1:40	95.2	95.6
H3N2		
%4-fold rise	79.5	**29.6**
% HI ≥ 1:40	95.2	97.3
B strain		
%4-fold rise	**4.4**	**36.8**
% HI ≥ 1:40	**5.5**	**38.5**

Source: Table 14.2.1A Mod5, Vol 2, Sect 16.2, Tables p10

Reviewer comment: A post-vaccination HI titer of ≥ 1:40 for H1 and H3 was met by children in both age groups. Children in Group B failed to demonstrate a 4-fold rise to

H3, but these children had pre-vaccination GMT of 262.8 and 77% had baseline titers of at least 1:40. These baseline parameters were much higher than for H1 and B strains and for the younger children. It is, therefore, not surprising that this group did not achieve a further 4-fold rise to the H3 strain in response to the booster dose. Immune responses to the B strain were weaker in both age groups, and particularly in the younger children. This weaker response has been observed for other trivalent influenza vaccines in both adults and children. Older children in Group B actually had a point estimate of 44.8% and just missed the LB for the 4-fold rise in titer against the B strain.

8.1.3.2.3 Safety Results CSLCT-FLU-04-05 – Booster Dose

- Of 273 children enrolled in the Booster study, only one was excluded from the safety evaluation. One subject in Group B received an incorrect half dose (0.25mL) of vaccine and was excluded from the analysis.

- Deaths – none.

- Serious Adverse Events

  In the 30 day post-booster vaccination period, 2 subjects experienced SAEs that were assessed as possibly related to vaccination:

  - Subject A069 (3 years of age) experienced fever to 40ºC (104ºF) and vomiting on the evening of vaccination and was admitted to the hospital for hydration. Throat swab for influenza was negative. The child fully recovered. The event was assessed as possibly related to the vaccine.

  - Subject A088 (3 years of age) experienced fever (to 38.8ºC, 101.8ºF) and vomiting on the evening of vaccination, and also had a febrile seizure. The seizure lasted 10 seconds and the child was described as non-responsive for 5-7 minutes afterwards. The child was taken to the ER and discharged with persistent fever (38.9ºC) after 2.5 hours of observation, and was reported as recovering fully.

  Six SAEs occurred in the 6-month period following booster vaccination. Review of case narratives and SAE forms suggests that none of these events were vaccine related:

  - A059 – 1 year old female with history of asthma and maintained on a salbutamol inhaler, received primary vaccinations on March 22, 2005 and April 21, 2005 without difficulty. She received the booster on March 9, 2006. On June 11, 2006, the subject was treated in an ER for URI and exacerbation of asthma. This was followed by 2 more exacerbations over the ensuing 5 days which resulted in admission to the hospital. Record indicates full recovery by July 10, 2006. Not related.

- A035 – 1 year old female who received dose 1on March 11, 2005, dose 2 on April 8, 2005, and a booster on March 10, 2006. Hospitalized on July 25, 2006 with acute gastroenteritis manifest by 2 days of fever, diarrhea, vomiting and lethargy. No diagnostic studies. Responding to hydration and supportive care. Discharged the following day. Completely recovered by August 2, 2006. Not related.

- A046 – 1 year old female received dose 1 on March 18, 2005, dose 2 on April 15, 2005, and a booster on March 6, 2006. Fever and lethargy on July 23, 2006, transient response to amoxicillin for suspected otitis media, but recurred and was hospitalized on July 30, 2006. Diagnosed with E. coli UTI, treated with IV antibiotics and resolved. Not related.

- B063 – 6 year old male received dose 1 on April 5, 2005, dose 2 on May 10, 2005, and was diagnosed with type 1 diabetes on June 27, 2005, considered unrelated. Received booster on April 4, 2006, and on July 5, 2006 was hospitalized with a hypoglycemic seizure. Responded to IV glucose, hydration, and insulin. EEG and EKG normal. Not related.

- A134 – 1 year old male received dose 1 on April 19, 2005, dose 2 on May 20, 2005, and the booster on April 26, 2006. Diagnosed with tonsillar and adenoid hypertrophy in September 2006 and was hospitalized for elective tonsillectomy/adenoidectomy on October 17, 2006. Discharged, recovered. In retrospect, parents had noted abnormal dribbling, rhinorrhea, wheezing, dysphonia, and snoring since October 15, 2005. Symptoms resolved post-operatively. Not related.

- A163 – 2 year old female received dose 1 on April 26, 2005, dose 2 on May 26, 2005, and booster on May 1, 2006. On July 2, 2006 (62 days post-vaccination), the subject was hospitalized with abdominal pain, viral pharyngitis and probable mesenteric adenitis. Diagnostic studies remarkable for leukocytosis, normal AXR. Responded to IV fluid, penicillin, and acetaminophen. Discharged July 4, fully recovered by July 7, 2006. Not related.

Table 8-24 SAEs following Booster Dose through Day 180 – CSLCT-FLU-04-05

Pt ID/ Group	SAE	Asso'd Dose	Time To onset (days)	Grade	Tx	Outcome	Rel
Events within 30 days of dose							
A069	Fever and vomiting	B	0	Severe	Hosp	Recovered	Poss
A088	Fever and vomiting	B	0	Severe	Hosp	recovered	Poss
Events occurring more than 30 days dose							
A059	Exacerbation of asthma	B	94	Severe	Hosp	recovered	No
A035	Viral gastroenteritis	B	137	Severe	hosp	recovered	No
A046	Urinary tract infection	B	139	Severe	hosp	recovered	No
B063	Hypoglycemic seizure	B	61	Severe	hosp	recovered	No
A134	Tonsillectomy/ Adenoidectomy	B	174	-	hosp	recovered	No
A163	Viral pharyngitis and Mesenteric adenitis	B	62	-	hosp	recovered	No

Reviewer comment: Of the 8 SAEs that occurred in the 180 days following booster vaccination, only 2, both fever and vomiting, appear to have been possibly related to the study vaccine. Fever and vomiting post-vaccination and febrile seizures are not uncommon occurrences in the pediatric population.

8.1.3.2.4 Solicited Adverse Events – Booster Dose

- Solicited AEs are summarized in (Table 8-24). For subjects with multiple occurrences of the same event, the maximum severity grade was used in the summary.

Table 8-25 Solicited Adverse Events – CSLCT-FLU-04-05 – Booster Vaccination

Solicited AEs	Group A, n=76				Group B, n=196			
	Gr 1	Gr 2	Gr 3	Total %	Gr 1	Gr 2	Gr 3	Total %
Local								
Pain	30	9	0	**51.3**	91	45	4	**71.4**
Redness	29	4	0	**43.4**	60	13	12	**43.4**
Swelling	16	3	0	**25.0**	34	5	12	**26.0**
Systemic								
Fever	21	5	4	**39.5**	28	17	8	**27.0**
Headache	0	0	0	**0**	32	12	5	**25.0**
Cough	16	1	0	**22.4**	30	3	0	**16.8**
Sore throat	4	1	0	**6.6**	17	3	0	**10.2**

Solicited AEs	Group A, n=76				Group B, n=196			
	Gr 1	**Gr 2**	**Gr 3**	**Total %**	**Gr 1**	**Gr 2**	**Gr 3**	**Total %**
Rhinitis	25	2	0	**35.5**	53	4	1	**29.6**
Wheezing/ Shortness of breath	2	0	1	**3.9**	4	5	0	**4.6**
Myalgia	4	1	0	**6.6**	15	8	0	**11.7**
Earache	1	0	0	**1.3**	2	0	1	**1.5**
Vomiting/diarrhea	8	3	2	**17.1**	9	14	4	**13.8**
Loss of appetite	12	3	1	**21.1**	20	7	6	**16.8**
Irritability	18	8	2	**38.2**	33	22	8	**32.1**

Source: Tables VII and VIII, Mod 5, Vol 2, Booster CSR p.45-46, and electronic datasets

Reviewer comment: The vast majority of reactogenicity events were mild in intensity. There were few severe events, and these occurred primarily in the older children. Injection site erythema and swelling, fever, irritability and loss of appetite were the most commonly reported severe events. Overall, the most common solicited AEs experienced by the Group A were injection site pain and erythema, fever, rhinitis, and irritability. The most common solicited symptoms among Group B subjects were local pain and erythema, irritability, rhinitis, fever, and headache.

8.1.3.2.5 Unsolicited Adverse Events – Booster

- A summary of unsolicited AEs by severity grade and vaccine-relatedness can be found in Table 8-25:

Table 8-26 Summary of Unsolicitied AEs – CSLCT-FLU-04-05 - Booster Vaccination

	Group A N=76		**Group B N=196**		**Total N=272**	
% of subjects Or events	**%n**	**E**	**%n**	**E**	**%n**	**E**
Parameter						
Any Unsolicited AE	47.4	72	39.3	153	41.5	225
Mild	28.9	36	19.4	62	22.1	98
Moderate	19.7	27	23.0	70	22.1	97
Severe	10.5	9	6.6	21	7.7	30
Serious AEs	0	0	1.0	2	1.0	1
Vaccine-related SAEs	0	0	1.0	2	1.0	1
Vaccine-related AEs	1.3	1	8.7	19	6.6	20
Discontinued due to AE	0	0	0	0	0	0
Discontinued due to SAE	0	0	0	0	0	0
Death due to AE	0	0	0	0	0	0

Source: Tables 14.4.2A and 14.4.3A, Mod 5, Vol 2, CSR (Booster), pp15-16, and electronic datasets

- 41.5% of all subjects experienced at least one Unsolicited AE, more younger (47.4%) than older (39.3%) children. Fewer than 11% of all events were assessed as severe in intensity. Two SAEs were considered vaccine-related. The majority of AEs were not considered vaccine-related.

Reviewer comment: evaluation of the electronic datasets revealed identical or nearly identical numbers as compared to the Applicant's report and summary tables. However, the electronic and tabular summary tables do not include Subject A088 as an SAE. This SAE was found only in the Booster Addendum report, CRFs, and SAE forms. Additionally, for Subject A069 who experienced an SAE of fever and vomiting, the SAE is coded as an ILI in the datasets, but as fever and vomiting in the Booster Addendum narratives and on the SAE form. The electronic datasets only included AE information collected through Day 30.

- Most frequently occurring Unsolicited AEs by System Organ Class and Preferred Term (Table 8-26):

Table 8-27 Unsolicited AEs Occurring in ≥ 5% of Subjects within 30 Days of Booster Vaccination – CSLCT-FLU-04-05

Adverse Event SOC and PT	**Group A N=76**		**Group B N=196**		**Total N=272**	
	n	%	n	%	N	%
Gastrointestinal ds	11	14.5	16	8.2	27	9.9
Vomiting	4	5.3	5	2.6	9	3.3
General and Admin Site disorders	11	14.5	17	8.7	28	10.3
Pyrexia	7	9.2	6	3.1	13	4.8
Infections and infestations	7	9.2	19	9.7	26	9.6
Nervous System Disorders	1	1.3	12	6.1	13	4.8
Headache	1	1.3	11	5.6	12	4.4
Respiratory, Thoracic ,& Mediastinal	17	22.4	33	16.8	50	18.4
Cough	12	15.8	18	9.2	30	11.0
Rhinorrhea	8	10.5	16	8.2	24	8.8

Source: Table 14.4.4A, Mod 5, Vol 2, CSR tables pp17-19, and electronic datasets

Reviewer comment: The most frequent Unsolicited AEs occurring in the 30 days after booster vaccination were: cough (15.8%), rhinorrhea (10.5%), pyrexia (9.2%) and vomiting (5.3%) in Group A; and cough (9.2%), rhinorrhea (8.2%) and headache (5.6%) in Group B.

- All Severe Unsolicited AEs by SOC and PT as determined by evaluation of the electronic datasets is presented in (Table 8-27):

Table 8-28 Summary of Severe Unsolicited AEs within 30 Days of Booster Vaccination – CSLCT-FLU-04-05

	Group A N=76	Group B N=196	Total N=272
Adverse Event SOC/PT	**N (%)**	**N (%)**	**N)%)**
Ear and labyrinth ds			
Ear pain	1	1	2
Gastrointestinal Disorders			
Diarrhea		1	1
Nausea		1	1
Vomiting	1	1	2
General and Administration Site disorders			
Feeling abnormal		1	1
ILI		3	3
Local swelling	1		1
Pyrexia	2		2
Infections and Infestations			
Bronchiolitis		1	1
Croup infectious	1	3	4
Nasopharyngitis		1	1
Tonsillitis		1	1
Injury, poisoning and Procedural complications			
Head injury	1		1
Nervous system disorders			
Headache		1	1
Psychiatric disorders			
Abnormal behavior*	1		1
Irritability		1	1
Respiratory, thoracic, and Mediastinal disorders			
Asthma/wheezing		1	1
Pharyngolaryngeal pain		1	1
Rhinorrhea	1		1

*preceded dose 1

Reviewer comment: There were relatively few severe unsolicited AEs overall, 27 among 272 subjects. Only 1 or 2 subjects experienced each event with the exception of ILI (n=3) and croup (n=4).

- AEs of Special Interest associated with either the primary or booster vaccinations were summarized in Section 8.1.2.3.5 of this review. No unusual hypersensitivity, neurologic, or autoimmune type events were reported after the booster vaccinations.

8.1.4 Comments and Conclusions Study CSLCT-FLU-04-05

- CSLCT-FLU-04-05 was not originally designed with a regulatory intent to support U.S. licensure of CSL's Inactivated Influenza Vaccine. The purpose of

- Overall, CSL's Inactivated Influenza Vaccine was associated with solicited local and systemic AEs which were mild to moderate in severity, predominantly vaccine-related, and not unexpected. Injection site pain and erythema, irritability, rhinitis, cough and fever were the most frequently reported solicited AEs overall, following either primary or booster vaccinations in both age groups. The frequency of vaccine-related Unsolicited AEs was reported as at most 11.6%. There were no unusual trends or safety signals noted among the Unsolicited AEs. No serious vaccine-related events occurred after primary vaccination, whereas 2 episodes of fever and vomiting regarded as serious and possibly related to the study vaccine followed booster vaccinations. There were no deaths or discontinuations due to AEs or SAEs. The study provided safety data at time points beyond 180 days post-vaccination. There were no new safety concerns identified in this study.

- Although relatively small in sample size, the safety data submitted in this study was used to support the licensure of Afluria in adults ≥ 18 years of age in September 2007, and supports licensure in the pediatric population 6 months to < 9 years of age at the present time. A post-marketing safety study in children 6 months to 18 years of age is ongoing.

- Regarding efficacy, the immunogenicity data presented by the applicant indicates that Afluria meets the FDA Guidance surrogate immunogenicity endpoint criteria after 2 doses in children 6 months to < 9 years of age. Relatively weaker immune responses to the B strain were observed following booster vaccination. A post-marketing immunogenicity study in children and adolescents began in September 2009 and will provide additional immunogenicity data in support of the pediatric indication.

9 Overview of Efficacy Across Trials

- One clinical study, CSLCT-FLU-04-05, has been submitted to support the proposal to extend the indication for Afluria from the "active immunization of persons 18 years and older against influenza disease caused by influenza virus subtypes A and type B present in the vaccine" to persons 6 months of age and older. Therefore, this section will briefly highlight the efficacy results of study CSLCT-FLU-04-05. The reader is referred to Section 8.1 for details.
- This section will also summarize clinical efficacy data in adults that was submitted and reviewed for the original Afluria BLA as supportive data for the pediatric indication.
- Preliminary immunogenicity and clinical endpoint data from ongoing post-marketing commitments is not yet available.

9.1 Methods

- For the original Afluria BLA, data from one Phase III pivotal study under U.S. IND and from four non-U.S. IND studies were presented by the applicant in support of efficacy. The pivotal study (CSLCT-FLU-05-09/DMID-06-0016) included only adult subjects ≥ 18 to < 65 years. Three of the remaining four studies (CSLCT-FLU-05-11, CSLCT-FLU-05-13, CSLCT-FLU-04-99) stratified subjects into two groups: ≥ 18 to < 60 and ≥ 60 years of age. The fourth non-IND study (CSLCT-FLU-05-15) evaluated subjects ≥ 65 years. For the purpose of licensure in the United States, subjects were stratified into two age groups: adults ≥18 to < 65 years and adults ≥ 65 years, and post hoc analyses were performed on subjects ≥ 65 years of age.

- In the original BLA, CSLCT-FLU-04-05 was submitted to support the safety database. Summaries of immunogenicity data were also presented by the applicant in tabular form. Electronic datasets were not submitted for CSLCT-FLU-04-05 with the original BLA. The reviewer evaluated source data which consisted of line listings.

9.2 Efficacy Endpoints

- Please also see the introduction to Section 8 of this review.

- The five studies submitted to the original BLA and CSLCT-FLU-04-05 used the Hemagglutinin Inhibition (HI) Assay to measure serum anti-HI antibody titers.

- The HI assay for the pivotal study CSLCT-FLU-05-09 was validated and was performed at the same ------(b)(4)---------- laboratory in the US as was the assay for study CSLCT-NHF-05-15. The HI assays for the other non-IND studies were performed by -------(b)(4)----------.

- The (b)(4) assay validation report and a --(b)(4)-- technical transfer (proficiency) report are provided with this BLA. An inter-laboratory comparability study was undertaken to determine the degree of correlation between the HAI assay results between the 2 laboratories used in the testing of CSL –sponsored vaccine studies. This study used test results from a panel of sera from 20 subjects in study CSLCT-NHF-05-13 (adults 18-60 years, 2006) that had been tested by both laboratories in 2006. The comparability study concludes that the HAI assay results from -------(b)(4)------- correlate well. The study report has been submitted with the pediatric application 125254/132. Please see Section 4 and the reviews by Dr Lev Sirota (Statistical Assay) Dr. Galina Vodeiko (Bioassay).

- Criteria for Assessment of Immune Response – please see the introduction to Section 8.

9.3 Study Design

- The following table compares the study design of studies submitted to the original BLA and the pediatric trial submitted with this BLA supplement (Source: Clinical Review Afluria BLA 125254/0):

Table 9-1 Study Design of Efficacy Trials Supporting BLA 125254

Study/ Date	Age group	N*	US IND/ Sites	Phase	Design
CSLCT-FLU-05-09 Jun 06-Aug 06	18to<65	1089	Yes 9 USA	III	Randomized 1:1:1:1:1 Double blinded Placebo control
CSLCT-NHF-05-15 Oct 06-Dec 06	≥65	206	No UK**	IV	Randomized 3:1 Observer blind Influsplit control
CSLCT-NHF-05-11 Oct 05-Nov 05	18to<60 ≥60	102 104	No UK	IV	Randomized 1:1 Observer blind Mutagrip control
CSLCT-NHF-05-13 May 06-Jun 06	18to <60 ≥60	60 60	No UK	IV	Open label Uncontrolled
CSLCT-NHF-04-99 May 05-Jun 05	18to <60 ≥60	60 60	No UK	III	Open label Uncontrolled
CSLCT-FLU-04-05 Mar 05-Jul 05	≥6mos <3yr ≥3yr to<9yr	151 147	No Australia	III	Open label Unblinded Uncontrolled

*N=number of subjects who received CSL IVV in each study

**The four non-IND studies were conducted at the same site, the ----------(b)(4)----------.

9.4 Efficacy Findings

- The following tables summarize the efficacy data from the five studies submitted to the BLA for Efficacy Review (based on BLA 125254/0 Tables Module 2 Volume 1 Section 2.5 and 2.7.3):

Table 9-2 Summary of Efficacy Results in Adults ≥18 to <60 years of age from Controlled Studies submitted to Original BLA STN 125254/0*

Study	A/H1N1		A/H3N2		B strain	
	%4-FI ** (LB)	% ≥ 1:40 (LB)	%4-FI (LB)	% ≥ 1:40 (LB)	%4-FI (LB)	% ≥ 1:40 (LB)
CSLCT-FLU-05-09 n=1077	48.7 (45.6)	97.8 (96.7)	71.5 (68.7)	99.9 (99.5)	69.7 (66.9)	94.2 (92.7)
CSLCT-NHF-05-11						
CSL IVV n=102	64.7 (54.6)	87.3 (79.2)	93.1 (86.4)	97.1 (91.6)	62.7 (52.6)	72.5 **(62.8)**
Mutagrip n=102	70.6 (60.7)	89.2 (81.5)	90.2 (82.7)	96.1 (90.3)	63.7 (53.6)	76.5 **(67.0)**
CSLCT-NHF-05-13 n=60	39.0 **(26.5)**	91.5 (81.3)	45.8 **(32.7)**	94.9 (85.9)	54.2 (40.8)	71.2 **(57.9)**
CSLCT-NHF-04-99 n=60	55.0 (42)	83.3 (71)	90.0 (79)	98.3 (91)	56.7 (43)	58.3 **(45)**

*for CSLCT-FLU-05-09 Adults ≥18 to <65 years of age
**4-FI=4-fold increase in HI titer to a minimum of 1:40
% ≥ 1:40 indicates the proportion with post-vaccination anti-HI titer ≥ 1:40
LB = lower bound of the 95% CI
Bold print indicates where results fail to meet FDA criteria for immune response of % 4-fold increase HI > 40% or post-vaccination HI titer ≥ 1:40 >70%.

- To present results for adults 65 years of age and older according to FDA immune response criteria, the applicant pooled data from the two comparator controlled studies. The integrated analysis appears below and is based on STN 125254/0 Table 2.7.3.3-17 in Module 2 Volume 1 Section 2.7.3 p 37:

Table 9-3 Integrated Analysis of Efficacy Results for Older Adults ≥65 years of age (Studies CSLCT-NHF-05-15 and CSLCT-NHF-05-11)

Treatment	H1N1		H3N2		B strain	
	%4-FI* (LB)	% ≥ 1:40 (LB)	%4-FI (LB)	% ≥ 1:40 (LB)	%4-FI (LB)	% ≥ 1:40 (LB)
CSL IVV N=266	35.3 **(29.8)**	78.9 (73.7)	54.1 (48.1)	97.7 (95.2)	44.7 (38.9)	77.0 (71.7)

*4-FI=4-fold increase in HI titer to a minimum of 1:40
% ≥ 1:40 indicates the proportion with post-vaccination anti-HI titer ≥ 1:40
LB = lower bound of the 95% CI
Bold print indicates where results fail to meet FDA criteria for immune response of % 4-fold increase in HI titer >30% or % post-vaccination HI titer ≥ 1:40 >60%.

- The lower bound of the 95% CI for the proportion with 4-fold increase in HI titer for the H1N1 strain just missed the endpoint criterion of ≥30%. The other endpoints were met for all three strains in this older population. Immunogenicity results for the active comparators in these small non-IND studies were very similar to CSL IVV, are not presented here, but may be found in the original BLA review.

9.5 Overview of Efficacy CSLCT-FLU-04-05

- CSLCT-FLU-04-05 was a Phase III, open-label, non-randomized, non-blinded trial conducted at two sites in Australia to evaluate the safety and immunogenicity of CSL's IVV in support of European licensure for a pediatric indication. A sample size of 300 was planned as specified by the Swedish Medical Products Agency (MPA). 151 subjects were enrolled in Group A (≥ 6 months to < 3 years) and 147 subjects were enrolled in Group B (≥ 3 years to < 9 years). Exclusion criteria included previous influenza vaccination. Subjects received 2 primary doses of vaccine 30 days apart: Group A 0.25 mL (7.5mcg HA per strain) and Group B 0.5 mL (15mcg HA per strain). A booster dose was administered approximately 12 months after the primary vaccination series. Serologies were obtained 30 days following each dose.

- Evaluable immunogenicity population at each stage of the study (Table 9-4):

Table 9-4 Evaluable Population and Immunogenicity Timepoints for CSLCT-FLU-04-05

Stage	Group A	Group B
Day 0 (pre-vaccination)	151	147
Day 30 (post-Dose 1)	143	144
Day 60 (post-Dose 2)	139	132
Day 365 (pre-Booster)	76*	197*
Day 395 (post-Booster)	61	174

*Any Group A subject who turned 3 years of age after Day 60 and the Booster dose was re-assigned to Group B

- Summary of immune responses to each dose by age and treatment group (Tables 9-5 and 9-6):

Table 9-5 Immune Response Endpoints Group A (≥6 mos to <3years)

	Group A (≥6 mos to <3years)			
Antigen/ Endpoint (LB 95% CI)	Criterion for Success	Post-Dose 1 N=143	Post-Dose 2 N=139	Post-Booster N=74
H1N1				
%4-fold increase	≥40	**11.3**	90.8	85.6
% HI ≥1:40	≥70	**11.3**	91.7	95.2
H3N2				
%4-fold increase	≥40	80.3	85.6	79.5
% HI ≥1:40	≥70	94.7	97.9	95.2
B strain				
%4-fold increase	≥40	**14.9**	89.9	**4.4**
% HI ≥1:40	≥70	**15.5**	91.7	**5.5**

N=Evaluable population for each dose
Bold type indicates failure to meet FDA immune response endpoint criteria

Table 9-6 Immune Response Endpoints Group B (≥3 years to <9 years)

	Group B ≥3 years to <9 years			
Antigen/ Endpoint (LB 95% CI)	Criterion for Success	Post-Dose 1 N=144	Post-Dose 2 N=132	Post-Booster N=192
H1N1				
%4-fold increase	≥40	**18.5**	89.3	66.3
% HI ≥1:40	≥70	**19.8**	91.2	95.6
H3N2				
%4-fold increase	≥40	61.1	63.2	**29.6**
% HI ≥1:40	≥70	95.7	97.8	97.3
B strain				
%4-fold increase	≥40	**26.2**	88.4	**36.8**
% HI ≥1:40	≥70	**27.5**	90.3	**38.5**

N=Evaluable Population for each dose
Bold type indicates failure to meet FDA immune response endpoint criteria

Reviewer comment: The tables demonstrate that, in both young and older children, the two dose primary vaccination series elicited strong immune responses that met co-primary endpoint criteria for all three vaccine strains. In addition, the vaccine elicited a response in the H3N2 strain that met endpoint criteria after the first dose.

Strong immune responses to H1N1 persisted after booster vaccination. Following booster vaccination, H3N2 did not demonstrate a 4-fold rise in titer, but the proportion with a post-vaccination titer of ≥ 1:40 was 97.3%. It may have been difficult to demonstrate another 4-fold rise to H3N2 in >40% of subjects when the previous titer had already been at least 1:40 in 97.8% of subjects following Dose 2. The explanation for the weak booster responses to the B strain in both age groups, and particularly in the younger children, is not clear. Historically, weak immune responses to the B strain have been noted in trials of other trivalent influenza vaccines. This has been true in both very young and elderly populations.

9.6 Efficacy Conclusions

- In the pediatric study CSLCT-FLU-04-05, both the younger and older age groups met both immune response endpoints recommended in the FDA May 2007 Guidance for all three strains after receiving 2 doses of vaccine. Immune responses to the B strain were weaker relative to H1 and H3 strains, especially in children 6 months to 3 years of age, but exceeded pre-specified endpoint criteria.

- Supportive data from the original BLA indicates that CSL IVV met all six surrogate efficacy endpoints in Adults ≥18 to <65 years of age in the pivotal Phase III study CSLCT-FLU-05-09 conducted in the US under BB-IND-(b)(4). Post hoc analyses of the four supporting non-IND studies examined subjects ≥65 years of age (n=343), applied FDA criteria for immunogenicity, and revealed lower immune responses to both the H1N1 and B strains. However, immune responses wane with age, and lower responses in the elderly are not unexpected. In these studies, very similar results were found for the US and EU licensed comparator influenza vaccine controls. Analyses of the non-IND studies were limited by the small sample sizes and wide confidence intervals.

- Overall, the immune responses induced by CSL IVV in the pediatric study CSLCT-FLU-04-05 and in the Phase III pivotal trial CSLCT-FLU-05-09 appear sufficient to reasonably predict clinical benefit in adults ≥18 to <65 years of age and in children 6 months to <9 years of age. Following accelerated approval, CSL agreed to conduct post-marketing studies to confirm adequate immunogenicity and protection against infection. These studies are ongoing. A culture confirmation study in healthy adults not at increased risk for complications of influenza (CSLCT-USF-06-28) was conducted in 2008-2009, and, because of a low attack rate, is scheduled to continue for a second season (2009-2010). A non-inferiority trial in the elderly (CSLCT-USF-07-41) was conducted in 2008-2009, and results are pending. Finally, CSL committed to conducting two post-marketing pediatric trials: an open-label pediatric safety study (CSLCT-USF-06-29, n=1992) began in March 2009; and a non-inferiority trial (CSLCT-USF-07-39, n=1350) began in September and will evaluate the immunogenicity of Afluria compared to US-licensed TIV in children 6 months to < 18 years of age.

- The original BLA contained adequate and well-controlled studies in the adult population, and, while efficacy in adults might be extrapolated to the pediatric population [21 CRF 314.55 (a)], CSLCT-FLU-04-05 was limited by a small sample size and an open-label design that did not control for safety. Therefore, at the time of the original BLA review, the review team took a conservative approach and deferred approval of a pediatric indication pending additional data from post-marketing commitments. Subsequent to that decision, at the present time, extenuating circumstances have changed the risk benefit ratio for the pediatric indication. Therefore, based on the strength of the available adult and pediatric immunogenicity data and on an altered risk benefit ratio, the Reviewer believes that Afluria should be granted accelerated approval in the pediatric population. This will be discussed further in Section 12, Overall Conclusions.

10 Overview of Safety Across Trials

10.1 Safety Database – Extent of Exposure

- The pediatric approval BLA supplement contains safety data from a single pediatric study CSLCT-FLU-04-05. The data reviewed in Section 8.1.2 (Results of Primary Vaccination Dose 1 and Dose 2) and Section 8.1.3 (Results of Booster Vaccination) will be presented as an integrated summary in this section. Please refer to Section 8 for the details of study CSLCT-FLU-04-05. The status of ongoing postmarketing pediatric studies CSLCT-USF-06-29 and CSLCT-USF-07-36 will be presented. The post-marketing pharmacovigilence data for CSL's thimerosal-free product will also be summarized.

- Because the pediatric safety data are considered distinct from adult data, the two databases will not be integrated. However, a brief summary of the adult data submitted to the original BLA will be presented as supportive information.

- The following table summarizes the safety database for the completed pediatric study by age and dose group:

Table 10-1 Pediatric Safety Database for CSL IVV

Study	Total N	Stage	Population for Safety Analysis		Total # of dose exposures*
			6 mos to <3 yr	**3 to <9 yr**	
CSLCT-FLU-04-05	298	Day 30 PostDose 1	151	147	298
		Day 60 Post Dose 2	143	144	287
		Day 365 PostBooster	75**	197**	272
Total	**298**		369	488	**857**

*This total includes multiple dose exposures per subject at the specified stage of study.
**Any subject in Group A who turned 3 years old during the period between the primary vaccination phase and the booster dose was re-assigned to Group B.

- Among the 298 participants in the study, there were a total of 857 doses of vaccine administered, 369 to children 6 months to < 3 years, and 488 to children 3 to < 9 years of age.

- Demographics – see Sections 8.1.2.1 and 8.1.3.2.1.

10.2 Significant/Potentially Significant Events

10.2.1 Deaths

- No deaths occurred in the 180 days following either primary or booster vaccinations.

10. 2.2 Serious Adverse Events

- A total of 21 SAEs occurred throughout the entire study period. During the 30-day post-vaccination periods following each dose, 3 SAEs occurred following primary Dose 1 or Dose 2, and 2 occurred following the Booster Dose. Of all the SAEs, only 2 appeared possibly related to the study vaccine: both of these were reported as fever and vomiting occurring on the evening of booster vaccination. One was associated with a febrile seizure. Both children were hospitalized for less than 24 hours and both fully recovered.

- Tabular summaries of all SAEs for CSLCT-FLU-04-05 are presented in Table 10-2 (SAEs following primary doses 1 and 2) and Table 10-3 (SAEs following booster doses). All SAEs were collected for 180 days following each vaccination. Please refer to Sections 8.1.2.3.2 and 8.1.3.2.3 for case narratives.

Table 10-2 Serious Adverse Events following Primary Dose 1 and Dose 2 through Day 180 – CSLCT-FLU-04-05

Pt ID/ Group	SAE	Asso'd Dose	Time To onset	Grade	Tx	Outcome	Rel
Events within 30 days of dose							
A013	RSV bronchiolitis	2	18d	Severe	hosp	Resolved	No
A124	Dehydration due to diarrhea	2	6	Severe	hosp	Resolved	No
B087	Picornavirus Pneumonia	1	0	Severe	MD	Resolved	No
Events occurring > 30 days through 180 days following Dose 2							
A106	UTI	2	35	Severe	Hosp	Resolved	No
B063	Type 1 diabetes	2	38	Severe	Hosp	Ongoing	No
A111	Asthma	2	37		Hosp		No
A006	Meningococcal sepsis	2	94	Severe	Hosp		No
B089	Autism spectrum Disorder	2	>90		HCP	Sx preceded Vax	No
A147	Laceration to mouth	2	87		Hosp		No
A022	Rotavirus gastroenteritis	2	41		Hosp		No
Off Study Period – between end of 6 month follow-up and 1 year Booster Dose							
A085	Exacerbation of asthma	2	>180		Hosp		No
B088	Exacerbation of asthma	2	>180		Hosp		No
B105	Asthma	2	>180		Hosp		

Rel=related. 1=Primary Dose 1. 2=Primary Dose 2. B=booster dose. HCP=health care provider

Table 10-3 SAEs following Booster Dose through Day 180 – CSLCT-FLU-04-05

Pt ID/ Group	SAE	Asso'd Dose	Time To onset (days)	Grade	Tx	Outcome	Rel
Events within 30 days of dose							
A069	Fever and vomiting	B	0	Severe	Hosp	recovered	Poss
A088	Fever and vomiting	B	0	Severe	Hosp	recovered	Poss
Events occurring more than 30 days dose							
A059	Exacerbation of asthma	B	94	Severe	Hosp	recovered	No
A035	Viral gastroenteritis	B	137	Severe	hosp	recovered	No
A046	Urinary tract infection	B	139	Severe	hosp	recovered	No
B063	Hypoglycemic seizure	B	61	Severe	hosp	recovered	No
A134	Tonsillectomy/	B	174	-	hosp	recovered	No

Pt ID/ Group	SAE	Asso'd Dose	Time To onset (days)	Grade	Tx	Outcome	Rel
	Adenoidectomy						
A163	Viral pharyngitis and Mesenteric adenitis	B	62	-	hosp	recovered	No

Rel=related. 1=Primary Dose 1. 2=Primary Dose 2. B=booster dose.

10.2.3 Adverse Events of Special Interest (AESI)

- AEs of Special Interest associated with either the primary or booster vaccinations are summarized in Section 8.1.2.3.5 of this review.

- The datasets were searched for terms that included: immune system disorders, hypersensitivity, drug hypersensitivity, adverse drug reaction, allergy, anaphylaxis, hives, urticaria, serum sickness, vasculitis, swelling, angioedema, allergic asthma, anemia, lymphadenopathy, thrombocytopenia, immune thrombocytopenia, arthralgia, myalgia, synovitis, rash, rash pruritic, conjunctivitis (for cases suggestive of oculorespiratory syndrome), acute disseminated encephalomyelitis, Guillain Barre Syndrome, myelitis, neuritis, and paraesthesia.
- No unusual hypersensitivity, neurologic, or autoimmune type events appeared to occur following either primary or booster vaccinations.

10.2.4 Discontinuations Due to AEs, SAEs, or other Medically Significant Events

- There were no discontinuations due to AEs, SAEs or other medically significant events associated with either primary or booster vaccinations.

10.3 Summary of Solicited AEs in the 7 Days following Primary or Booster Vaccinations (Table 10-4)

Table 10-4 Summary of Solicited AEs in the 7 Days following Primary or Booster Vaccinations – CSLCT-FLU-04-05

	Group A %* 6 mos to < 3 years			Group B % 3 to < 9 years		
Event	**Dose 1 N=151**	**Dose 2 N=151**	**Booster N=76**	**Dose 1 N=147**	**Dose 2 N=147**	**Booster N=196**
Local						
Pain	36.4	37.1	51.3	59.2	61.9	71.4
Erythema	35.8	37.7	43.4	36.7	45.6	43.4
Swelling	15.9	20.7	25.0	24.5	27.2	26.0
Systemic						
Irritability	47.7	41.1	38.2	20.4	17.0	32.1
Rhinitis	37.1	47.7	35.5	21.1	28.6	10.2
Fever	22.5	22.5	39.5	15.6	8.2	27.0

	Group A %* 6 mos to < 3 years			Group B % 3 to < 9 years		
Event	**Dose 1 N=151**	**Dose 2 N=151**	**Booster N=76**	**Dose 1 N=147**	**Dose 2 N=147**	**Booster N=196**
Cough	21.2	31.8	22.4	19.0	19.0	29.6
Loss of appetite	19.2	23.8	21.1	7.5	5.4	16.8
Vomiting/ Diarrhea	14.6	13.9	17.1	7.5	6.8	13.8
Headache	2.0	3.3	0.0	13.6	10.9	25.0
Myalgia	0.7	2.7	6.6	13.6	8.2	11.7
Sore throat	2.0	5.3	6.6	8.2	10.9	16.8
Wheezing/SOB	3.3	8.6	3.9	2.7	2.0	4.6
Earache	3.3	3.4	1.3	4.1	1.4	1.5

SOB=shortness of breath

Reviewer comment: Overall, the most common solicited AEs experienced by both age groups following any dose, were injection site pain and erythema. Younger children (Group A) also reported more rhinitis, irritability, fever, cough, vomiting and diarrhea relative to older children. Older children (Group B) were more likely to report headache and myalgia than younger children. As noted in Sections 8.1.2.3.3 and 8.1.3.2.4, the vast majority of reactogenicity events were mild in intensity.

Wheezing/shortness of breath was reported in relatively more children in Group A following Dose 2. This did not recur with the Booster Dose, nor was this event noted in a disproportionate number of subjects in Group B. Most of the events were assessed as mild. Most of these children had a past history of asthma, wheezing, or bronchiolitis. Wheezing, bronchiolitis and asthma occur commonly in young children, and none of the reported events appeared to be associated with a hypersensitivity reaction or anaphylaxis. For further discussion, please see Section 8.1.2.3.3.

10.4 Summary of Unsolicited AEs that Occurred in the 30 Days Following any Dose in either Age Group (Table 10-5)

Table 10-5 Summary of Unsolicited AEs Occurring in ≥ 5% of all Subjects in the 30 Days following Primary or Booster Vaccinations – CSLCT-FLU-04-05

	Group A %* 6 mos to < 3 years			**Group B % 3 to < 9 years**		
System Organ Class/ Preferred Term	**Dose 1 N=151**	**Dose 2 N=151**	**Booster N=76**	**Dose 1 N=147**	**Dose 2 N=147**	**Booster N=196**
Infections and infestations						
Nasopharyngitis	5.3	7.9	3.9	5.4	5.4	4.1
Rhinitis	13.2	9.9	2.6	6.8	10.9	0.0
URI	9.9	7.3	1.3	6.1	6.1	1.0
Psychiatric disorders						
Irritability	3.3	5.3	2.6	0.7	0.7	2.0
Nervous system disorders						
Headache	1.3	0.7	1.3	6.1	4.1	5.6
Respiratory, thoracic and Mediastinal disorders						
Cough	10.6	13.2	15.8	10.9	13.6	9.2
Rhinorrhea	7.3	6.0	10.5	6.8	4.8	8.2
Gastrointestinal disorders						
Teething	14.6	9.9	3.9	0.0	0.0	0.0
Vomiting	5.3	2.6	5.3	2.0	2.7	2.6
General and Administration site conditions						
Influenza-like illness	13.9	10.6	2.6	6.8	3.4	2.6
Pyrexia	2.6	9.3	9.2	2.7	4.1	3.1

URI=upper respiratory tract infection

10.4 Ongoing Pediatric Clinical Studies

Afluria was granted approval for use in adults 18 years and older on the condition that CSL conduct post-marketing studies in children. The following studies are in progress:

- CSLCT-USF-06-29 – open-label, multi-center study to evaluate safety in children 6 months to < 18 years of age conducted in Australia March 6, 2009 to July 17, 2009. A total of 1992 subjects were enrolled and stratified into the following age groups:
    - 6 mos to < 3 years (n=710)
    - 3 to < 9 years (n=880)
    - 9 to < 18 years (n=402)

- This study is in the 6 month SAE follow-up phase. One SAE of asthma has occurred in this study, and it was considered unrelated to the study vaccine. There have been no deaths.

- CSLCT-USF-07-36 – a randomized, observer-blind, multicenter, non-inferiority comparison of immune response of Afluria versus US licensed TIV. Objectives are to demonstrate a non-inferior immune response relative to the comparator, safety and tolerability. Enrollment began the first week in September. 1,350 children are to be stratified 1:1:1 according to age:

  - Cohort A: 6 months to < 36 months, n = 450
  - Cohort B: 3 years to < 9 years, n = 450
  - Cohort C: 9 years to < 18 years, n = 450

10.5 Summary of Safety Data Supporting the Original Afluria BLA STN 125254/0

- Adult data collected as part of CSL's clinical development program and submitted to the adult licensure application will not be reviewed or considered for the pediatric license application because the indications are considered distinct. However, this data is summarized below for completeness and as supportive information in a general sense. It is important to note that the safety profile for Afluria has been similar to other US-licensed trivalent influenza vaccines. No safety signals were observed in the data submitted to STN 125254/0.

- Five adult studies were submitted to STN 125254/0. Additionally, an integrated summary of 23 small older Australian studies were submitted to enhance the safety database:

Table 10-6 Summary of Exposure to CSL IVV in Clinical Studies 1992-2006

Group	6mos to<9yr	18 to <60 yrs	≥60 yrs	≥65 yrs*	**TOTAL**
Adults Thimerosal-Free		763	670	378	**1433**
Adults with Thimerosal		1719	706	522	**2425**
Pediatric Thimerosal-free	298				**298**
TOTAL	**298**	**2482**	**1376**	**900**	**4156**

*Subjects ≥65 years are a subset of those ≥60 years

- In the original BLA, the Applicant reported a total number of 4156 subjects exposed to CSL's trivalent influenza vaccine in the clinical safety database from

- In addition to the 5 primary adult studies submitted to support the BLA, the Applicant submitted an integrated safety analysis from 23 older studies to further enhance the database. These were studies conducted in Australia between 1992 and 2000 primarily to support registration, and included both controlled and uncontrolled trials. Nineteen of these used thimerosal-containing vaccine and 4 used thimerosal-free vaccine. Studies conducted before 1997 did not capture Unsolicited AEs.

10.6 Safety Data from Afluria Post-Marketing Commitments

- SAE reports for the post-marketing studies in healthy young adults (CSLCT-USF-06-28) and in adults ≥ 65 years of age (CSLCT-USF-07-41) submitted to IND (b)(4) have not raised new safety concerns. Similarly, the most recent post-marketing commitment Annual Report, IND (b)(4) Amendment #94, covering the period May 10, 2008 to May 9, 2009, did not identify a safety signal. Included in the report was data from the four Afluria Post-Marketing Commitments:

    - CSLCT-USF-06-28 – culture confirmation study in young healthy adults
    - CSLCT-USF-07-41 – elderly non-inferiority study
    - CSLCT-USF-06-29 – pediatric open label safety study
    - CSLCT-USF-07-36 – pediatric non-inferiority study

- To briefly summarize the May 2008-2009 Annual Report:

    - Solicited and Unsolicited AEs for the reporting period were not unusual for a trivalent inactivated influenza vaccine.

    - SAE reports did not raise new safety concerns. Only one SAE, asthma, has occurred in a child.

    - New Onset of Chronic Illness reporting was notable for the following autoimmune type conditions that either began or worsened following vaccination: ulcerative colitis, rheumatoid arthritis, sacroiliac joint arthritis, Grave's Disease, hypothyroidism (n=2), and Bell's Palsy. Of these, only ulcerative colitis was considered possibly related to Afluria. This does not appear to be excessive or unusual for an enrollment of 15,545 subjects, 8,278 of whom have completed study procedures. None of these events involved children or adolescents.

    - Post-marketing surveillance for Afluria for this period (UK, EU, Australia, SE Asia) resulted in IND Safety Reports that included 3 cases of GBS, one case of ulcerative colitis, 1 unexplained sudden death, 1 hypersensitivity reaction, one episode of asthma, and 1 seizure. Assessment of these

- There were 4 deaths in the adult studies, all appeared unrelated to Afluria. There were no deaths or dropouts in the open-label pediatric safety study during the reporting period. The pediatric non-inferiority study had not yet begun enrollment during the reporting period.

- Overall, the PMC Annual Report did not raise new safety concerns for a trivalent influenza vaccine.

10.7 Other Safely Findings

10.7.1 Laboratory and Special Diagnostic Studies – not applicable

10.7.2 Vital Signs, Physical Examinations – not applicable

10.7.3 Drug Interactions

- Studies evaluating drug-drug interactions or simultaneous administration with other vaccines have not been conducted. The Applicant states that there have been no reports of adverse interactions with other vaccines to date.

10.7.4 Use in Pregnancy and Lactation – no clinical data are available in this regard.

10.8 Post-Marketing Surveillance

- CSL has been manufacturing trivalent inactivated influenza vaccine by essentially the same process since 1968 except for eliminating thimerosal in 2002. CSL's thimerosal-free pre-filled syringe presentation was licensed for persons 6 months of age and older by the Australian Therapeutic Goods Administration (TGA) in November 2002 under the tradename Fluvax. Since 2002 CSL has distributed approximately ---(b)(4)--- thimerosal-free doses of vaccine worldwide, primarily in Australia, the United States and Europe. CSL's IVV is currently registered in 26 countries outside the US. In Europe, CSL IVV is also licensed in persons 6 months and older.

- The Applicant provides a summary of its thimerosal-free IVV database which includes and does not distinguish between reports received for CSL IVV and other unknown TIV. The summary covers the period from November 2002 to April 30, 2009.

- Total reports, all age groups = 844. Of these, 241 were serious. Most frequent reports were ILI and injection site reactions.

- Total report for children and adolescents < 18 years = 77. Of these, 28 were serious. Of the 77 AEs, 27 were pyrexia, 10 were accidental overdose or exposure (majority reported no adverse outcome), and the remaining were miscellaneous. The majority of events were transient and mild.

- The post-marketing surveillance monitors specifically for serious neurologic disorders (e.g., GBS, transverse myelitis), immune system disorders (serum sickness), and interaction with warfarin. There have been no reports of these type of events in persons < 18 years of age thus far.

- The post-marketing surveillance data in children and adolescents suggests a safety profile for Afluria that is similar to adults and to other TIV, and that has not identified new or unusual safety concerns thus far.

10.9 Safety Conclusions

- The safety database for children and adolescents consists primarily of data from CSLCT-FLU-04-05 in which 298 children 6 months to < 9 years of age were administered a total of 857 primary and booster doses of vaccine and were followed for 180 days after each dose. Injection site pain and erythema were the most common adverse events following vaccination. Younger children appear to experience relatively more fever and influenza-like symptoms than older children. Two SAEs may have been related; both were occurrences of fever and vomiting following the booster dose of vaccine. There were no deaths or discontinuations due to AEs. Spontaneous post-marketing reports are consistent with the clinical study results. No unusual new trends or safety signals were identified in the pediatric study CSLCT-FLU-04-05, in the interim Annual Report from the pediatric safety PMC CSLCT-USF-06-29, or in post-marketing surveillance from November 2002 to April 30, 2009.

- Overall, the data suggests that Afluria has an acceptable safety profile and a favorable risk benefit ratio in children and adolescents.

- Limitations of the data are that CSLCT-04-05 was a small study and did not include a control group. While these limitations do not have a great impact on the immunogenicity data, the small sample size may have lessened our ability to detect rare SAEs, and the absence of a control group makes it more difficult to place very frequent AEs in the proper context. A control group may have been helpful, for example, in evaluating the disproportionate wheezing that occurred in Group A following Dose 2. However, while the data are not ideal, they are overall satisfactory and will be enhanced by the 2 large post-marketing commitments that are currently in progress.

11 Additional Clinical Issues

11.1 Directions for Use, Dosage and Administration

- Afluria (CSL IVV) is a sterile suspension for intramuscular (IM) injection. Each 0.25mL dose contains 7.5µg of HA and each 0.5mL dose contains 15µg of HA from each of the three influenza virus strains included in the vaccine.

- Afluria is supplied in three presentations:

    - 0.25 mL preservative-free, single-dose, pre-filled syringe
    - 0.5 mL preservative-free, single-dose, pre-filled syringe
    - 5 mL thimerosal-containing multi-dose vial, each containing 10 doses. Each 0.5mL dose contains 50 mcg thimerosal (24.5mcg mercury) added as a preservative.

- Children 6 months through 35 months of age (0.25mL dose by IM injection):
    - Previously unvaccinated children should receive two 0.25mL doses; one on day 1 and a second approximately 4 weeks later.
    - Previously vaccinated children should only receive one 0.25mL dose.

- Children 36 months through 8 years of age (0.5mL dose by IM injection):
    - Previously unvaccinated children should receive two 0.5mL doses; one on day 1 and a second approximately 4 weeks later.
    - Previously vaccinated children should only receive one 0.5mL dose.

- Children 9 years of age and older (0.5mL dose by IM injection):
    - A single 0.5mL dose for IM injection.

11.2 Special Populations – other populations not applicable to this supplement.

11.3 Pediatrics

The Pediatric Research Equity Act (PREA) of 2003 requires that clinical studies be conducted in children for biological products under development. There must be adequate data to support safety and effectiveness, dosing and administration in this population. Effectiveness may be extrapolated from adequate and well-controlled studies in adults provided that the data is supplemented by safety and surrogate endpoint studies in children. Pediatric studies in the BLA process may be deferred as long as a post-marketing commitment to conduct Phase IV trials is made.

The pediatric development plan was addressed during the original BLA review. The Pediatric Review Committee (PeRC) agreed with the review team's plan to defer pediatric studies and to conduct the aforementioned post-marketing studies in children and adolescents 6 months to < 18 years of age. With this BLA

supplement, the accelerated approval for Afluria would be extended to persons 6 months and older on the basis of surrogate endpoint data extrapolated from adults, and on the immunogenicity and safety data in children 6 months to < 9 years reported in study CSLCT-FLU-04-05. Traditional approval will be contingent upon acceptable results from the ongoing clinical endpoint study in adults, and the safety and non-inferiority studies in children and adolescents.

12 Overall Conclusions:

- In the pediatric study CSLCT-FLU-04-05, after receiving 2 primary doses of vaccine, children 6 months to < 9 years of age met both immune response endpoints recommended in the FDA May 2007 Guidance for all three vaccine strains. Immune responses to the B strain were weaker relative to H1 and H3 strains, especially in children 6 months to 3 years of age, but exceeded pre-specified endpoint criteria.

- Overall, the surrogate endpoint immune responses induced by CSL IVV in the pediatric study CSLCT-FLU-04-05 and in the Phase III pivotal trial CSLCT-FLU-05-09 appear sufficient to reasonably predict clinical benefit in adults ≥18 to 65 years of age and in children 6 months to <9 years of age. These data can be extrapolated to children and adolescents 9 to <18 years of age.

- The safety database for children and adolescents consists primarily of data from CSLCT-FLU-04-05 in which 298 children 6 months to < 9 years of age were administered a total of 857 primary and booster doses of vaccine and were followed for 180 days after each dose. Injection site pain and erythema were the most common adverse events following vaccination. Younger children appear to experience relatively more fever and influenza-like symptoms than older children. Two SAEs possibly related to the vaccines were reported: both were occurrences of fever and vomiting following a booster dose of vaccine. There were no deaths or discontinuations due to AEs. No unusual new trends or safety signals were identified in the pediatric study CSLCT-FLU-04-05, in the interim Annual Report from the pediatric safety PMC CSLCT-USF-06-29, or in post-marketing surveillance from November 2002 to April 30, 2009.

- Limitations of the data are that CSLCT-04-05 was a small study and did not include a control group. While these limitations so not have a great impact on the immunogenicity data, the small sample size may have lessened our ability to detect rare SAEs, and the absence of a control group makes it more difficult to place very frequent AEs in the proper context. However, while the data are not ideal, they are overall satisfactory and will be enhanced by the two larger post-marketing commitments.

- Overall, the data submitted to this Prior Approval BLA Supplement suggests that Afluria is safe and immunogenic in children 6 months to < 9 years of age, and that

13 Recommendations

13.1 Approval

- CSLCT-FLU-04-05 was submitted to the original Afluria BLA in support of safety. The original BLA contained adequate and well-controlled studies in the adult population, and, while efficacy in adults might be extrapolated to the pediatric population [21 CRF 314.55 (a)], CSLCT-FLU-04-05 was limited by a small sample size and an open-label design that did not control for safety. Therefore, at the time of the original BLA review, the review team took a conservative approach and deferred approval of a pediatric indication pending additional data from post-marketing commitments. Subsequent to that decision, at the present time, extenuating circumstances have changed the risk benefit ratio for the pediatric indication. Therefore, based on the strength of the available adult and pediatric immunogenicity data and on an altered risk benefit ratio, the Reviewer believes that Afluria should be granted accelerated approval in the pediatric population.

- Re-assessment of the risks and benefits of granting accelerated approval to Afluria in the pediatric population was prompted by two major factors: First, in 2008, the ACIP expanded its recommendations for annual influenza vaccination to include children 5 to <18 years of age. The availability of another thimerosal-free influenza vaccine could fulfill an unmet medical need in this population and provide meaningful clinical benefit. Second, and of greater urgency, is the current 2009 H1N1 pandemic that has disproportionately affected children and young adults. Children are among those prioritized to receive the monovalent H1N1 pandemic vaccine at the earliest possible time. At present, there is only one thimerosal-free seasonal inactivated trivalent influenza vaccine approved for use in children 6 months to 3 years of age. Accelerated approval of Afluria for use in children 6 months to < 18 years of age could expand the availability of a seasonal TIV in this age group, especially in the youngest children at greatest risk for complications of influenza. Additionally, the regulatory pathway for approval of CSL's monovalent 2009 H1N1 pandemic vaccine in children could be facilitated by an approved seasonal vaccine in this age group. An approved pediatric indication would permit approval of the H1N1 vaccine in children as a strain change as has been done for adults, and would obviate the need for an Emergency Use Authorization in the pediatric population.

- The Clinical Review Team recommends that Afluria be granted approval in children 6 months to < 18 years of age because of newly recognized potential clinical benefit that outweigh known risks. Accelerated approval could be granted

13.2 Recommendation on Postmarketing Actions

- As part of the accelerated approval of Afluria in adults in September 2007, CSL agreed to conduct post-marketing studies to confirm adequate immunogenicity in relevant populations and to confirm protection against infection in healthy adults. These studies are ongoing. A culture confirmation study in healthy adults not at increased risk for complications of influenza (CSLCT-USF-06-28) was conducted in 2008-2009, and, because of a low attack rate, is scheduled to continue for a second season (2009-2010). A non-inferiority trial in the elderly (CSLCT-USF-07-41) was conducted in 2008-2009; results are pending. Two post-marketing pediatric trials are also in progress: an open-label pediatric safety study (CSLCT-USF-06-29, n=1992) that began in March 2009; and a non-inferiority trial (CSLCT-USF-07-39, n=1350) that began in September and will evaluate the immunogenicity of Afluria compared to US-licensed TIV. Both pediatric PMCs include children 6 months to < 18 years of age.

- In the PAS the Applicant has acknowledged that accelerated approval of Afluria in children 6 months to < 18 years of age is contingent upon completion of the post-marketing studies.

13.3 Labeling

The Package Insert (PI) submitted by the Applicant is in the format required by FDA's Final Rule titled "Requirements on Content and Format of Labeling for Human Presecription Drug and Biological Products" published in January 2006. Specific comments on the revised labeling (not included in this review) were conveyed to the Applicant. Revisions were agreed upon in a final round of negotiations on November 5, 2009. The Applicant submitted a final package containing the final revised package inserts (for the seasonal and pandemic influenza type A (H1N1) 2009 monovalent vaccines) and labeling for cartons and containers on November 9, 2009. Please also see the Labeling section of the Summary Basis for Regulatory Action memo.

Appendix 1 – Immunogenicity Analyses by Gender (provided by Dr. Massie)

Table 8) Efficacy Response Stratified by Gender and Age Group

Strain/ Endpoint	**FDA criteria**	**Group A ≥6mos to <3yrs**		**Group B ≥3yrs to <9yrs**	
		N=149		N=147	
	Lower bound 95% CI	**Males n= 73**	**Females n= 76**	**Males n= 66**	**Females n= 81**
H1N1					
% 4-fold increase *	>40%	91.5%	86.6%	80.0%	89.9%
% with HI ≥ 1:40**	>70%	91.6%	85.3%	80.0%	87.4%
H3N2					
%4-fold increase	>40%	95.8%	90.6%	84.6%	93.6%
% with HI ≥1:40	>70%	84.7%	83.5%	58.7%	66.3%
B Strain					
% 4-fold increase	>40%	92.7%	87.9%	84.6%	88.7%
% with HI ≥ 1:40	>70%	92.7%	87.9%	84.6%	87.9%