Title Page and General Information

BLA number: 125254
Related IND numbers: 12997
Reviewer Name, Division, and Mail Code:
Clinical Reviewer: Cynthia Nolletti, MD. CBER/OVRR/DVRPA/Clinical Trials Branch, HFM-485.
Supervisory Reviewer: Joseph Toerner, MD, Team Leader, HFM-475
Draft Review Completed: August 29, 2007

Final Review Completed: September 19, 2007

Submission Received by FDA: March 30, 2007

1.2 Product
1.2.1 Established Names:
Influenza virus vaccine

Proprietary or trade names referred to in this BLA and considered equivalent drug product: Afluria, Fluvax, Enzira, Influenza Vaccine-CSL Limited, and CSL Influenza Virus Vaccine (CSL IVV).

1.2.2 Proposed Trade Name: Afluria

1.2.3 Product Formulation:
The 2007-2008 vaccine contains HA from three influenza strains:
- A/Solomon Islands/3/2006 (H1N1) 15µg
- A/Wisconsin/67/2005/ (H3N2) 15µg
- B/Malaysia/2506/2004 15µg

Total 45µg HA antigen

The product is supplied in two presentations:
- Preservative-free pre-filled syringe for single use
- Thimerosal-containing multi-dose vials
Each 5mL vial contains 10 doses.
Each 0.5mL dose contains 50µg thimerosal (24.5 µg mercury)

Afluria contains the following 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 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 Indication:

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.

1.6 Proposed Population(s): Adults 18 years of age or older.

1.7 Dosage Form and Route of Administration:

45µg influenza antigen (15µg per strain) per 0.5mL dose administered intramuscularly.

2.0 Table of Contents

3.0 Executive Summary

o The trivalent inactivated split virion egg-based influenza vaccine Afluria (CSL IVV) should be approved for the active immunization against influenza disease caused by influenza subtypes A and type B contained in the vaccine in adults 18 years of age and older. The recommendation for accelerated approval is based on demonstration of efficacy by a surrogate endpoint: the immune response following administration of CSL IVV. 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. There were no patterns of unusual safety concerns associated with administration of CSL IVV. Other European studies provided additional immunogenicity and safety data following administration of CSL IVV that support this approval. Therefore, the potential benefits of administration of CSL IVV are well-balanced against the potential risks. With this accelerated approval, the availability of an additional trivalent influenza vaccine provides meaningful benefit in the setting of established shortages of influenza vaccine.

o The license application also included safety and immune response source data from four adult studies conducted in the United Kingdom. These studies enrolled 652 subjects that received CSL IVV, 343 of which were 65 years of age or older. Post hoc analyses from active controlled studies demonstrated that immune responses to CSL IVV were acceptable in the geriatric age group. Two small uncontrolled open-label studies revealed lower immunogeniciy in the geriatric population. However, two active controlled studies showed similar immune responses between CSL IVV and the comparator influenza vaccine among subjects 65 years of age or older, and immune response data from studies of three other U.S. licensed trivalent influenza vaccines have also demonstrated lower immune responses in the

elderly. Therefore, additional immune response data support an extension of the approved indication to adults 65 years of age and older.

o The application's overall safety database included source data from 1089 healthy adults in the pivotal study and 652 older adults, 343 of whom were 65 years of age or older, from the UK studies. To enhance the safety database, the applicant provided a small uncontrolled open-label pediatric study as well as an integrated analysis of safety data from 23 older studies in adults conducted in Australia, for a total safety database of 4156 CSL IVV recipients. There were no new safety concerns identified on review of these data or in the review of more recent post-marketing spontaneous adverse event reports. A post hoc analysis of the 65 years and older population from the four supporting non-IND studies did not reveal safety issues unique to this age group.

o There were no apparent differences in safety or immunogenicity between the thimerosal-free and preservative-containing formulations.

o The proposed dosing regimen is a single 0.5mL dose, containing 15µg of influenza antigen for each of the three vaccine strains, administered intramuscularly in the region of the deltoid muscle of the upper arm.

o Overall, the methodology, integrity of the data, and results of the safety and immunogenicity assessments support approval of the license application.

o The applicant has committed to conduct postmarketing studies in healthy adults to demonstrate efficacy against culture-confirmed influenza illness as supported by the surrogate endpoint of immune response. The applicant will also conduct a non-inferiority study of Afluria against a U.S. licensed trivalent influenza vaccine in the geriatric population. Finally, the application included source data from an uncontrolled study of 298 children which revealed satisfactory immune response and safety parameters. The applicant will pursue its pediatric development plan as required under the Pediatric Research Equity Act with two postmarketing pediatric studies, one open-label and one non-inferiority, to be conducted with due diligence.

4 Significant Findings from Other Review Disciplines

4.1 Chemistry, Manufacturing and Controls (CMC):

Please refer to the review by Dr. Galina Vodeiko.

4.2 Animal Pharmacology/Toxicology:

The BLA did not contain a Nonclinical Overview or nonclinical study reports on the components of the trivalent influenza vaccine. CSL has supplied the vaccine since 1968, before the introduction of nonclinical safety/toxicology requirements. At the pre-IND

meeting between CBER and CSL held on February 22, 2005, it was agreed that no specific pre-clinical studies were required for this vaccine licensure because:

- CSL has extensive experience with the vaccine in humans over the last twenty years including 29 clinical studies and post-marketing safety data from approximately 34 million doses, 15 million containing 0.01% thimerosal and 19 million thimerosal-free.
- The vaccine is very similar to other trivalent inactivated split-virion influenza virus vaccines licensed in the US
- The composition of the vaccine has remained essentially unchanged for the past twenty years, with no new excipients or adjuvants. The removal of thimerosal has been the only significant change.

4.3 Statistics

- Please refer to the Statistical Reviews by Drs. Tammy Massie and Lev A. Sirota. Dr. Sirota reviewed the HI antibody assay validation procedures and found these procedures to be adequate. This clinical review contains some analyses performed by Dr. Massie and will be so referenced. Dr Massie's analyses of the electronic datasets revealed results and trends similar to the applicant. The Statistical Review supports approval of CSL IVV in adults 18-65 years of age, but has concerns relating to lower immune responses in the elderly. The Clinical Review will address these concerns.

4.4 Bioresearch Monitoring Branch (BIMO)

- BIMO conducted inspections of the pivotal study sites and found no significant problems that impacted the data submitted to the BLA
- Please see the review by Bhanu Kannan, BIMO

5 Clinical and Regulatory Background

5.1 Disease or Health-Related Conditions Studied and Available Interventions:

Influenza infection is caused by RNA viruses of which 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. 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 new antigenic variants or viral strains which result from point mutations in the viral

genome that occur during replication. This antigenic change is called antigenic drift and occurs more frequently in influenza A than in influenza B. 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.

Antigenic variants or strain changes occur each year necessitating yearly change in the formulation of the trivalent influenza vaccine for optimal protection. Although an exact correlate of immune protection is not known, previous experience with strain-specific immune response in the form of anti-hemagglutinin antibody titers appears to predict a clinical endpoint of efficacy with reasonable certainty. Previous experience with inactivated trivalent influenza vaccines suggests that anti-hemagglutinin titers might be used as a surrogate endpoint.

Influenza A and B causes illness in approximately 5% to 10% of adults annually with higher attack rates in children. Complications and death rates from influenza are highest in persons $\geq$ 65 years of age, children < 2 years of age, and persons of any age with certain chronic medical illnesses. Approximately 226,000 excess hospitalizations per year are attributed to influenza, with 63% occurring in persons $\geq$ 65 years of age.

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 resistance, adverse drug reactions, and the need for dose adjustments in 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. This includes children 6 to 59 months of age, pregnant women, and persons 50 years of age and older.

There are two types of licensed influenza vaccines available in the United States: trivalent inactivated vaccine (TIV) and live attenuated influenza vaccine (LAIV). Both are manufactured by growing influenza virus in chicken eggs. LAIV is currently approved for use only in healthy persons aged 5 to 49 years. Vaccine efficacy is dependent on a number of variables including age and host immunity, but to date the only available culture confirmation of efficacy is with LAIV in children, where absolute efficacy of 90% or greater has been observed. For TIV, when vaccine and circulating viruses are antigenically similar, vaccination is estimated to be approximately 70-90% effective in preventing influenza illness among young healthy adults < 65 years of age. Efficacy is lower, estimated to be 30-70%, among persons with underlying illnesses, those $\geq$ 65 years of age, or residing in nursing homes. However, prevention of influenza-related hospitalization or pneumonia may be 50-60% in these populations. The efficacy of TIV in children has ranged from 22% to 91% in various small

retrospective studies.

5.2 Important Information from Pharmacologically Related Products, Including Marketed Products

There are currently four licensed trivalent inactivated influenza vaccines in the United States: Fluarix (GSK), FluLaval (GSK**,** formerly ID Biomedical), Fluvirin (Novartis), and Fluzone (Sanofi Pasteur). These are approved for use in adults. In addition, Fluvirin is approved for use in children 4 years of age or greater, and Fluzone is approved for use in persons 6 months of age and older. Fluarix and FluLaval do not have a pediatric indication. FluMist (MedImmune) is the only licensed LAIV in the U.S., and is currently approved for use only in healthy persons aged 5 to 49 years.

Each year the World Health Organization (WHO) recommends three representative antigenic viral strains, H1N1, H3N2, and B, to be included in the trivalent vaccine for the upcoming influenza season. The recommendations are based on surveillance which tries to predict which strains will be circulating in each hemisphere.

5.3 Previous Human Experience with the Product Including Foreign Experience

o 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 --. 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. Today, the thimerosal-free vaccine is registered in 22 countries outside the United States including Europe, South Africa, South America, and Southeast Asia. The applicant reports that approximately --------- doses of thimerosal-free CSL IVV have been distributed globally between February 2003 and August 2006, for a total of -------------- doses distributed worldwide since 1985.

Reviewer comment: By comparison, at the time of Fluarix accelerated approval, approximately ------------n doses had been distributed worldwide since the early 1990's.

o Afluria has been manufactured by the same process for the last 20 years and, except for eliminating thimerosal in 2002, it is the same product now as it was in 1985. The safety database includes 29 clinical studies and post-marketing surveillance:

The pivotal Phase III study CSLCT-FLU-05-09 conducted in the US under BB-IND----------;

The four supporting non-IND studies reviewed in Section 8, Clinical Studies, of this review: 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 includes

approximately ---------- thimerosal-containing vaccine doses distributed from June 1997 to July 2002 and approximately ---------- thimerosal-free doses distributed from November 2002 to April 2006.

- The applicant reports a total of 4066 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. Details of the safety database will be presented in the Clinical Trials and Overview of Safety sections of this review. The most common reactogenicity events reported among the studies submitted to the BLA and the integrated summaries of previous clinical trials appeared to be injection site pain, tenderness, and erythema, and headache, malaise, and myalgia. Common unsolicited adverse events included headache, nasal congestion, rhinorrhea, cough, and pharyngolaryngeal pain.

- Prior to the pivotal study CSLCT-FLU-05-09 conducted under U.S. IND, 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.

  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.

  Immunogenicity data from this previous human experience is reviewed in detail in the Clinical Trials and Overview of Efficacy across Trials sections of this review.

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 BLA to support the safety database. Although not specifically requested, summaries of immunogenicity data in tabular form and source data consisting of line listings were also presented by the applicant.

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

- 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. In response, CBER developed a Draft Guidance for Industry that provided sponsors with clearly defined regulatory pathways for licensure of trivalent inactivated influenza vaccine including guidance on an accelerated approval pathway. The final version of this document, "Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines," was published by CBER in May 2007.

- Request for BLA Priority Review and Accelerated Approval

In 1992 the FDA published regulations (Federal Register Dec 11, 1992,57 FR 58958) under which the Agency would grant priority review of new drugs or biologics for serious or life-threatening illnesses. The Code of Federal Regulations (CFR) subpart H 21CFR314.500 and CFR314.510 further described the indications for 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.

o 21 CFR 314.500: **Scope**. This subpart applies to certain biological products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).

o 21 CFR 314.510: **Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.** FDA may grant marketing approval for a biological product on the basis of adequate and well-controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical endpoint to ultimate outcome. Post-marketing studies would usually be already underway. When required to be conducted, such studies must also be adequate and well controlled. The applicant shall carry out any such studies with due diligence.

o 21 CRF 314.530: Marketing approval for biological products approved under these regulations may be withdrawn, for example, if the postmarketing clinical study fails to verify clinical benefit or the sponsor fails to perform the required postmarketing study with due diligence.

o For the purposes of accelerated approval of seasonal inactivated influenza vaccines, the HI antibody response may be an acceptable surrogate marker of activity that is reasonably likely to predict clinical benefit. To date, prospective studies have not identified a specific HI antibody titer associated with protection against culture confirmed influenza illness. Some studies have suggested that HI antibody titers ranging from 1:15 to 1:65 may be associated with protection from illness in 50% of subjects, and protection from illness is increased with higher titers. Seroconversion and GMT have been uses as measures of vaccine activity. The laboratory assay used to measure the HI antibody response is dependent on a number of variables, and thus requires appropriate controls and assay validation for proper interpretation.

o To be considered for accelerated approval, a BLA for a new seasonal inactivated influenza vaccine should include results from one or more well-controlled studies designed to meet immunogenicity endpoints and a commitment to conduct confirmatory postmarketing studies of clinical effectiveness in preventing influenza during the next influenza season.

o The option to pursue an accelerated approval pathway for seasonal inactivated influenza vaccines is also available to sponsors if a shortage of influenza vaccine exists for the U.S. market at the time the new vaccine is approved. Influenza is a serious and sometimes life-threatening illness. Vaccination is the principal means of preventing influenza and its complications. Providing prophylaxis to those who would not otherwise be immunized during a shortage does provide a meaningful benefit over the then-existing treatments which are in short supply at that time.

o 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. These recommendations target high risk individuals, their caregivers, and household contacts. A goal of universal vaccination targeting 100% of the US population is set for 2008 and will require 300 million doses of influenza vaccine.

o There are four inactivated virus vaccines approved for use in the U.S.: Fluarix (GSK); FluLaval (GSK); Fluvirin (Chiron); and Fluzone (Sanofi Pasteur). There is one live virus vaccine approved for use in the U.S.: FluMist (MedImmune). Production for the US market averages approximately 83 million doses per year. According to the CDC, for the 2006-2007 season 120.9 million doses were produced, of which 102.5million doses were distributed according to demand. One million doses went into a government stockpile, and 17 million were unsold and discarded. For the 2007-2008 season, the U.S. is projected to have 127 million doses (Sanofi Pasteur 50 mil, Novartis 40 mil, GSK 30-35 mil, MedImmune 7 mil).

o CSL aspires to mitigate the shortage of vaccine by entering the US market with two presentations of the influenza vaccine: a single-dose, preservative free, 0.5 mL pre-filled syringe and a thimerisol-containing 5 mL multi-dose vial. At present, less than 20% of the projected 2007/2008 supply will be thimerosal-free. In the future, CSL plans to offer predominantly preservative-free, pre-filled syringes due to increasing demand for thimerosal-free vaccines. If accelerated approval for CSL's vaccine is granted, they hope to produce Afluria for the US 2007/2008 flu season, fulfilling an unmet need for prophylaxis against a potentially life-threatening disease. Although these data were not provided in the BLA submission, the sponsor estimates that they will be able to manufacture approximately ---------- doses of thimerosal-free pre-filled syringe product and ---------- doses of thimerosal-containing multidose vial product for launch in the US for the 2007/2008 season.

o On April 10, 2006 CSL Limited submitted BB-IND ---------- for a Phase III randomized, placebo-controlled, multi-center study to evaluate the immunogenicity, safety, and tolerability of its trivalent inactivated influenza vaccine, Afluria, in adults ages 18-65. This study was intended to be the pivotal study in clinical development towards a BLA. Trials supporting earlier phases of development had been conducted in Australia and the United Kingdom. The vaccine was initially distributed in Australia in 1968, and has since then been registered in 22 countries worldwide.

o CBER approved BB-IND -------- and conveyed clinical comments to CSL on June 12, 2006 which indicated that the sponsor's plans to use HAI titers as a surrogate endpoint for efficacy might support licensure under accelerated approval. The sponsor was asked to commit to conducting a clinical endpoint study in healthy adult subjects during the influenza season following accelerated approval of the license application. In addition, FDA recommended that CSL propose a plan for clinical development in the pediatric population. The Agency acknowledged that accelerated approval, 6 month review, might be appropriate for this vaccine if a shortage of influenza vaccine was anticipated at the time of application.

o CSL completed the Phase III pivotal study CSLCT-FLU-05-09 under BB-IND ----------, and, on January 3, 2007, submitted a pre-BLA package to CBER. A Type B face-to-face pre-BLA meeting between CSL and FDA was held on February 9, 2007. Non-IND studies which might support the safety and immune response database were agreed upon and were to be submitted with the BLA:

CSLCT-NHF-05-15
CSLCT-NHF-05-11
CSLCT-NHF-05-13
CSLCT-NHF-04-99
CSLCT-FLU-04-05
Integrated safety data from 23 earlier Australian studies

o FDA requested and the sponsor agreed to conducting three post-marketing studies: 1) a placebo-controlled culture confirmation study in healthy adults to be conducted during the influenza season following accelerated approval; 2) a non-inferiority study using a U.S. licensed comparator vaccine in adults ≥65 years of age and/or in adults ≥ 18 years of age with chronic medical conditions placing them at risk for complications of influenza, and; 3) a comparator-controlled study using a U.S. licensed vaccine in a pediatric population adequately powered to demonstrate non-inferior immune responses as outlined in CBER's Draft Guidance for Industry on Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines. FDA requested that draft protocols for these three studies be submitted with the BLA and that the final protocols be submitted to IND ---------- for review and comments. During the meeting, a case definition of ILI was agreed upon, and six month safety data for SAE's and unanticipated visits to health providers was requested for the post-marketing studies. The exclusive use of the thimerosal-free pre-filled syringe presentation of Afluria for post-marketing studies conducted in Australia was felt to be reasonable provided that the pivotal study results for this presentation were found to be comparable to the multi-dose vial presentation.

o In a telecon between CSL and FDA on August 9, 2007, the applicant clarified their agreement to conduct four postmarketing studies:

• Detailed synopses or drafts of all four protocols were to be submitted to both IND ---------and to the BLA by August 31, 2007.
• Clinical Endpoint Efficacy Study: will be a placebo-controlled trial in healthy adults in whom vaccination is not universally recommended to be initiated March 2008 and completed August 2008 in the Southern Hemisphere. Planned CSR Q2

2009. The primary endpoint will be culture-confirmed influenza illness. If the influenza attack rate is lower than expected, participant enrollment will be extended to a second season.

• At-Risk Adult Study: will be a non-inferiority immunogenicity study in adults ≥18 years of age who have chronic medical conditions placing them at risk for complications of influenza or who otherwise fall into groups for whom vaccination is recommended. The comparator control will be a U.S. licensed trivalent inactivated influenza vaccine (TIV). The study will begin in August 2008 and end in September 2008 in the Northern Hemisphere.

• Pediatric Studies: there will be two pediatric studies. The Pediatric Open-Label Study will begin March 2009 and end June 2009. The Pediatric Non-inferiority Study will begin August 2009 and end September 2009, and will compare CSL IVV to a U.S. licensed TIV control.

• CBER clarified for CSL that all four postmarketing studies are part of the accelerated approval conditions and are not viewed as an independent clinical development plan.

6 Clinical Data Sources, Review Strategy and Data Integrity

6.1 Material Reviewed

6.1.1 The Clinical Review of BLA submission STN 125254/0 focused on the following modules and volumes:

- Module 1 Volume 1, administrative information
- Module 2 Volume 1 and 2, overviews of clinical safety and efficacy
- Module 5 Volumes 1-30. This included the final protocol and final Clinical Study Report (CSR) for the pivotal study CSLCT-FLU-05-09 and the CSR's for the four supporting non-IND studies in adults. Line listings and electronic datasets (using JMP software) for the pivotal study and the four non-IND studies in adults were reviewed. The fifth non-IND study included in Module 5 was a pediatric study. The CSR and source data line listings for safety and immune responses were reviewed. Electronic datasets were not submitted for the pediatric study.
- The applicant provided integrated safety summary data (no source data) from 23 early Australian studies to enhance the safety database.
- Amendments to the BLA and to IND ------- including 15-day SAE reports were reviewed.
- Responses to FDA questions and requests for information were reviewed.
- The specific clinical studies submitted to the BLA were reviewed and are listed in Section 8 Clinical Studies below.

6.1.2 Literature

Betts, RF, O'Brien, D, Menegus, B, et al. A comparison of the protective benefit of influenza (FLU) vaccine in reducing hospitalization of patients infected in FLU A or FLU B. Clin Infect Dis. 1993; 17: 573.

Centers for Disease Control and Prevention. Prevention and Control of Influenza. Recommendations of the Advisory

Committee on Immunization Practices (ACIP). MMWR Morbidity and Mortality Weekly Report. 2006; 55(RR-10): 1-42.

de Jong, JC, Palache, AM, Beyer, WEP, Rimmelzwaan, GF, Boon, ACM, Osterhaus, ADME. Haemagglutination-inhibiting antibody to influenza virus. Developmental Biology (Basel). 2003; 115: 63-73.

FDA Guidance for Industry: Clinical Data needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines, May 2007.

Goodwin, K, Viboud, C, et al. Antibody response to influenza vaccination in the elderly: a quantitative review. Vaccine. 2006; 24: 1159-1169.

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.

Kaye, Donald, ed. U.S. to Have 127 Million Flu Vaccine Doses. CID 2007: 44 (15 June), iv.

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

Tunstall, R. Americans and Britons: Key Population Data from the Last Three U.S. and U.K. Censuses. Brookings and London School of Economics Comparative Urban Analysis Series. Feb 2005. URL: http://www.brookings.edu/metro/pubs/20050208_tunstallsurvey.htm.

United States Census 2000. Overview of Race and Hispanic Origin. U.S. Department of Commerce. Economics and Statistics Administration. U.S. Census Bureau. March 2001.

6.1.3 Post-Marketing Experience (non-US)

- The post-marketing experience in countries where CSL has marketing authorization for CSL IVV was summarized by the applicant in Module 5 and was reviewed as were the CRF's and SAE report forms submitted to IND -------. The applicant's draft Risk Management and Pharmacovigilence Plans also summarized the post-marketing experience and were reviewed.
- Review of the post-marketing experience is found in Section 10 of this review, Overview of Safety across Trials.

6.2 Table of Clinical Studies

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 vaccine
**The four non-IND UK studies were conducted at the same site, the Chiltern Research Center, in Slough, England, just west of London.

- CSL's split virion, inactivated trivalent influenza vaccine (CSL IVV) is marketed under several different trade or proprietary names worldwide including: 'Fluvax', 'Enzira', 'Afluria', 'Influenza Vaccine-CSL Limited', and 'CSL Limited Inactivated Influenza Vaccine'. These trade names appear throughout this review and are considered equivalent drug product. Where possible, the generic term CSL IVV is used in place of the trade name.

6.3 Review Strategy

- Data from the US pivotal study and all five non-IND studies submitted to the BLA were reviewed. In addition, the applicant's summary of integrated safety data from 23 older studies was reviewed. Subjects were analyzed according to age, and for purposes of licensure in the US, a post hoc immunogenicity analysis was performed on subjects 65 years of age and older.

- Data from the clinical study reports, line listings, and electronic datasets were reviewed and compared. ---- datasets were evaluated using ------ software program. The rates of adverse events and results of immunogenicity parameters were calculated from the datasets. These results were compared further with analyses performed by the Statistical Reviewer.

- Case report forms and SAE forms from the primary studies submitted to the BLA as well spontaneous post-marketing SAE reports submitted to IND --------- were reviewed for the safety analyses.

6.4 Good Clinical Practices (GCP) and Data Integrity

- The pivotal study CSLCT-FLU-05-09/DMID 06-0016 was conducted under US IND -------- in collaboration with the National Institutes of Health. The study was conducted in accordance with applicable regulatory requirements from the USA Code of Federal Regulations (CFR) and the International Conference on Harmonization (ICH) guidelines on Good Clinical Practice. On July 23, 2007, a preliminary Bioresearch Monitoring (BIMO) assessment from field investigations of the clinical sites suggested that the data had good integrity.
- Clincal 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.
- The non-IND studies conducted in the UK and submitted to the BLA were conducted under the Medicines and Healthcare products Regulatory Agency

(MHRA) Clinical Trial Authorization system and in accordance with the following guidelines:

National Health and Medical Research Council (NHMRC) "National Statement on Ethical Conduct in Research Involving Humans" (1999)
CPMP/ICH/135/95 "Note for guidance on Good Clinical Practice."
CPMP/ICH/377/95 "Note for guidance on Clinical Safety Data Management: definitions and standards for expedited reporting.
Declaration of Helsinki (June 1964, modified 1996 and 2002).
EU Clinical Trial Directive 2001/20/EC.

6.5 Financial Disclosures

- Dr. Russell Basser, Global Director of Clinical Development, CSL Ltd, acknowledged that none of the participating clinical investigators had any financial arrangements or interests related to the study product to disclose.

7 Human Pharmacology

- Since 1977, antigenic variants of influenza A (H1N1 and H3N2) and influenza B viruses have been circulating globally in humans. 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 there is no exact correlation, serum HI titers of 1:40 or greater have been associated with protection against influenza in up to 50% of subjects. Higher levels of antibody may be required for complete protection in older adults.
- 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-05-09/DMID 06-0016 (US BB IND ----------
CSLCT-NHF-05-15
CSLCT-NHF-05-11
CSLCT-NHF-05-13
CSLCT-NHF-04-99
CSLCT-FLU-04-05
Integrated safety data from earlier studies which included:

- CSLCT-FLU02-86
- CSLCT-FLU-00-77
- CSLCT-FLU-99-67
- CSLCT-FLU-98-57

- CSLCT-FLU-97-53
- CSLCT-FLU-96-48

Efficacy assessments

The clinical studies with CSL IVV have assessed humoral immunogenicity primarily using the HI assay, and clinical endpoint studies of efficacy have not been conducted. 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 will be conducted post-licensure in accordance with 21CRF 601.41.

For the pivotal study, CSLCT-FLU-05-09/DMID 06-0016, BB-IND --------, immunogenicity endpoints were based on the FDA criteria as described in the aforementioned FDA guidance. The non-IND studies, however, were 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. 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 the applicant 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
- An overall pass for the CPMP are based on at least one of the three immunogenicity criteria being met 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.

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
  - For studies CSLCT-FLU-05-09 and CSLCT-NHF-05-15, the HI assay was performed at ----------. The applicant states that the assay was validated in accordance with ICH Guideline Q2B *Validation of Analytical Procedures: Methodology* and FDA Guidance for Industry *Bioanalytical Method Validation*. ----------' validation package for the HI assay specific to the 2006 Southern Hemisphere influenza vaccine and A/Hiroshima/52/2005 for study CSLCT-FLU-05-09 is provided in Module 5 Section 5.3.5.5 of the BLA.
  - For studies CSLCT-NHF-05-11, CSLCT-NHF-05-13, and CSLCT-NHF-04-99, the HI assay was performed by ----------.
  - For details of the assay validation, please see the reviews by the Product Reviewer, Dr Vodeiko, and the Assay Statistical Reviewer, Dr Sirota. Dr. Sirota reviewed the statistical reasoning and calculations supporting validation of the Hemagglutination Inhibition test in the BLA submission and found no major issues that would prevent approval of the application.

8.1.1 Trial #1

8.1.1.1 Applicant's Protocol Number CSLCT-FLU-05-09 (BB-IND ---------, DMID 06-0016) "A Phase III, Randomized, Double-blind, Placebo Controlled, Multicenter Study to Evaluate the Immunogenicity, Safety and Tolerability of CSL Limited Inactivated Influenza Virus Vaccine in Adults ≥ 18 years to < 65 years.

8.1.1.1.1 Objective/Rationale:

Primary objective:
- To demonstrate that vaccination with CSL Influenza Virus Vaccine (CSL IVV) produces an immune response in young adults sufficient to meet FDA requirements for accelerated approval for licensure: that the proportion of subjects with a post-vaccination four-fold increase in HI titer to a minimum of 1:40 exceeds 40% and that the proportion of subjects with a post-vaccination HI antibody titer ≥1:40 exceeds 70%.

Secondary objectives:
- To demonstrate clinical consistency among the three lots of CSL IVV multidose vial presentation (thimerosal-containing),

- To demonstrate clinical consistency between CSL IVV multidose vial presentation (thimerosal-containing) and CSL IVV pre-filled syringe presentation (thimerosal-free), and

• To demonstrate acceptable safety and tolerability of CSL IVV multidose presentation (thimerosal-containing) and CSL IVV pre-filled syringe presentation (thimerosal-free).

8.1.1.1.2 Design Overview:

The study was a Phase III randomized, double-blind, placebo controlled, multicenter trial conducted at nine investigational sites in the United States 12 June 2006 to 25 August 2006. On Visit 1, Vaccine Administration Day 0, informed consent was obtained, and subjects were screened with medical history, physical exam, baseline anti-HI antibody, and pregnancy test. After meeting eligibility criteria, up to 1350 healthy adults ≥ 18 to ≤65 years of age were randomized 1:1:1:1:1 to one of five groups to receive 1 of 3 lots of thimerosal-containing CSL IVV in multidose vial, single lot thimerosal-free CSL IVV in a pre-filled syringe, or single lot placebo (vaccine diluent containing 0.01% w/v thimerosal) in a multidose vial. 0.5mL of study vaccine containing 15 μg antigen of each of the three WHO recommended strains of influenza virus for the 2006 Southern Hemisphere or 0.5 mL of placebo were administered intramuscularly in the deltoid muscle.

Post vaccination, subjects were observed for 30 minutes for immediate hypersensitivity or other adverse events (AE's). 5-day Solicited local and systemic AE diary cards and 21-day Unsolicited AE diary cards were issued.

Visit 2, Day 5 (window 5-7): review of 5-day Solicited AE memory aid, All Solicited and Unsolicited AEs/SAEs recorded, medication review.

Visit 3, Day 21 (window 21-24), Exit Evaluation: anti-HI antibody titers, review of 21-day Unsolicited AE diary card, assessment of any SAE's, medication review, targeted physical exam.

Table 8.1.1-1 Study Procedures and Assessments CSLCT-FLU-05-09

Study Visit	**Screen* 0**	**1**	**2**	**3**	**Early Termination**
Study Day	**-28 to -1**	**0**	**5-7**	**21-24**	
Procedure					
Obtain Informed Consent	X				
Review Eligibility Criteria	X	X			
Review Influenza Illness and Vaccination History	X	X			
Review Health Status				X	X
Oral Temperature, Blood Pressure and Heart Rate	X	X			
Medical History	X	X			
Targeted Physical Examination, as indicated	X	X		X	X
Urine or Serum Pregnancy Test	X†	X†			
Concomitant Medications	X	X	X	X	X
Blood for Antibody Assays		X†		X	X
Randomization		X			

Vaccination		X			
Distribute Memory Aid and Study-related Materials		X			
Review Memory Aid			X	X	X
SAE Assessment		X	X	X	X
AE Assessment		X	X	X	X

* At the discretion of the investigator, an optional screening period may be employed to provide adequate time for enrollment and consent procedures prior to vaccination. If the screening period was not utilized by the investigator, these assessments occurred on Day 0.

† For all female subjects of childbearing potential. Test with negative results must be obtained within 24 hours prior to vaccination.

8.1.1.1.3 Population

Planned enrollment was 1250 (up to 1350) healthy adult male and female volunteers ≥ 18 to < 65 years old at nine investigational sites in the United States (US). Subjects were stratified by age, with approximately 925 subjects aged ≥ 18 to <50 and approximately 325 aged ≥ 50 to < 65. A minimum of 63 subjects in the age range of 50 to 64 years was required in each group.

Inclusion Criteria:

- Healthy males or non-pregnant females (as indicated by a negative urine or serum pregnancy test immediately prior to vaccination), aged ≥ 18 to < 65 years at the time of providing informed consent.
- Provision of written informed consent to participate in the study and willingness to adhere to all Protocol requirements.
- In good health as determined by vital signs, medical history, and a targeted physical examination based on medical history.
- Able to understand and comply with planned study procedures.
- Females of non-childbearing potential or, if of childbearing potential, must be abstinent or agree to use adequate contraception for two months after vaccination.

Exclusion Criteria:

- Known hypersensitivity to a previous dose of influenza vaccine or allergy to eggs, chicken feathers, neomycin, polymyxin, thimerosal, or any components of the study vaccines.
- Vaccination against influenza in the previous 6 months.
- Underlying medical condition for which influenza vaccination was recommended; chronic heart or lung condition including asthma; metabolic disease; kidney disease; blood disorder; or weakened immune system including Human Immunodeficiency Virus (HIV)/Acquired Immunodeficieny Syndrome (AIDS).
- Acute clinically significant pulmonary, cardiovascular, hepatic, or renal functional abnormality.
- History of Guillain Barre Syndrome.
- Clinical signs of active infection and/or an oral temperature of ≥ 38ºC (100ºF). Study entry could be deferred for such individuals at the discretion of the PI.
- History of neurological disorders or seizures, with exception of a single febrile seizure during childhood.
- Confirmed or suspected immunosuppressive condition (including cancer), or a previously diagnosed immunodeficiency disorder (congenital or acquired).
- Receiving (within the 90 days before receiving the study vaccines)

immunosuppressive or immunomodulative therapy, systemic corticosteroids, and including the following:

- Chronic corticosteroids: >15mg/day of oral prednisone or equivalent daily;
- Sporadic corticosteroids: >40mg/day of oral prednisolone or equivalent for more than 2 courses of >14 days in the 3 months preceding vaccination;
- Immunoglobulins and/or any blood products within the 3 months preceding the administration of the study vaccine or during the study.

• Participation in a clinical trial or use of an investigational compound within 30 days before receiving the study vaccine or plans to enter a study during the study period.
• Vaccination with a registered vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to receiving the study vaccine.
• Currently treated with cytotoxic drugs or at any time during the 6 months before administration of the study vaccines.
• Major congenital defects or serious chronic illnesses.
• Evidence or history of (within the previous 12 months) drug or alcohol abuse.
• Unwilling or unable to comply with the study Protocol.
• History of psychiatric disorders that, in the opinion of the PI, would prevent the subject from giving proper informed consent or otherwise interfere with the study.
• Resident of nursing home or long-term care facility.
• Any condition that, in the opinion of the PI, would prevent the subject from complying with all aspects of the protocol or would put the subject at unnecessary risk.

Procedures not allowed: Use of investigational products during the study period, immunosuppressive therapy, blood products, and other vaccines as noted above.

Safety Population: the set of subjects used for the analysis of the safety data consisted of all subjects who received a dose of Study Vaccine on Day 0.

Evaluable Population: The set of subjects used for the analysis of the immunogenicity data consisted of all subjects who were vaccinated with Study Vaccine on Day 0, provided both pre- and post-vaccination blood samples, and were not excluded according to the use of any contraindicated medications.

Per Protocol Population: The set of subjects used for the per-protocol analysis of the immunogenicity data consisted of all subjects in the Evaluable Population who did not experience any significant protocol deviations, which could be thought to potentially have an effect on the immunogenicity assessments.

8.1.1.1.4 Products mandated by the protocol:

A 0.5mL dose of CSL IVV was administered once on Day 0 intramuscularly (IM) in the deltoid muscle. All forms of the study vaccine contained the three WHO recommended strains of influenza virus for the 2006 Southern Hemisphere:

- 15 µg A/New Caledonia/20/99 (IVR-116) (H1N1) strain
- 15 µg A/New York/55/2004-NYMC X-157 (H3N2) strain
- 15 µg B/Malaysia/2506/2004 strain

A total of 45 µg HA.

Afluria Lot numbers: Lots 556041N13, 556041N14, 556041N15 (multidose vials). Lot 556042N16 (pre-filled syringe).

Afluria contained the following 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 sodium phosphate
- 20 µg potassium phosphate
- 20 µg potassium chloride
- 1.5 µg calcium chloride

Placebo, 0.5 mL administered once IM on Day 0, contained:

- ----------
- ----------
- ----------
- ----------

Placebo Lot Number: Lot ----------

8.1.1.1.5 Endpoints

• Co-primary endpoints were:

o the lower bound of the 95% CI for the proportion of subjects with an increase in HI antibody titer of at least 4-fold, to a minimum post-vaccination HI titer of 1:40, was to exceed 40%; and

o the lower bound of the 95% CI for the proportion of subjects with post-vaccination HI antibody titers ≥1:40 was to exceed 70%.

Reviewer comment: In this study the applicant uses the term "seroconversion" to describe the proportion of subjects with a four-fold increase in HI titer to at least 1:40. This is consistent with the FDA definition of seroconversion for HI antibody. However, because some of the studies submitted to the BLA have a more restricted definition for seroconversion and also use the term "significant increase" for a four-fold rise in titer, in order to avoid confusion, we will use the phrase "proportion of subjects with an increase in HI antibody titer of at least 4-fold with a minimum post-vaccination HI titer of 1:40" throughout this BLA review to indicate both seroconversion or significant increase in HI titer. Similarly, the applicant uses the term "seroprotection" to define the proportion of study vaccine recipients with post-vaccination HI antibody titers greater than or equal

to 1:40. Because there is currently no established immunologic correlate of protection, FDA will avoid the use of this term with respect to this endpoint and describe as "proportion (or %) post-vaccination HI antibody titer ≥1:40".

Reviewer comment: the co-primary endpoints represent surrogate endpoints felt to be reasonably likely to predict clinical benefit. They were selected for use in lieu of the clinical endpoint of influenza illness as part of the accelerated approval process which is being sought because of an anticipated influenza vaccine shortage. Approval under these conditions is justified by the potential for serious and life-threatening influenza illness which might occur during a vaccine shortage in unvaccinated individuals for whom the vaccine is indicated. Approval is subject to the applicant's commitment to post-marketing studies using a clinical endpoint. The immune response criteria are now established in the FDA "Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines", May 2007, and are based on the EMEA "Note for Guidance on Harmonisation of Requirements for Influenza Vaccines". CPMP/BWP/214/96, March 1997.

Reviewer Comment: the pre-defined criteria for success were more robust in comparison to the EMEA immunogenicity criteria. The EMEA requires that only one endpoint be achieved in order to be considered successful and the endpoints are based on point estimates rather than the lower bound of the 95% CI. The use of the HI antibody titers was reasonably likely to predict clinical benefit.

- Validation of the HI assay

As stated in Section 8 above, the product and statistical reviewers found the HI antibody validation procedures to be acceptable. Therefore, the clinical reviewers found the results of the HI antibody determinations in studies CSLCT-FLU-05-09 and CSLCT-NHF-05-15 to be fully capable of demonstrating clinical benefit, and successful results would be acceptable for regulatory approval.

The principles of the assay are as follows: On the surface of the influenza virus, there are multiple copies of the major glycoprotein HA that binds specifically to sialic acid-containing receptors, such as those found on the plasma membrane of red blood cells. When red blood cells are incubated with the influenza virus in the appropriate ratio, the virus bridges the cells, causing hemagglutination. Specific attachment of antibody from serum samples, to antigenic determinants on the virus HA protein interferes with this binding and inhibits hemagglutination.

Prior to testing, the sera are treated to inactivate the non-specific inhibitors of viral hemagglutination and the virus HA antigen is standardized to the required number of HA units. The test itself is performed by mixing the standardized virus antigen with serial dilutions of test serum. The reciprocal of the highest dilution causing complete HI is a measure of the antibody level to that virus antigen under test.

• Secondary immunogenicity endpoints were to demonstrate lot-to-lot consistency by comparison of Geometric Mean Titers (GMT) to influenza Hemagglutinin antigens after vaccination of the active treatment arms:

- o Between the 3 lots of Afluria multidose vials and between Afluria multidose vials and the pre-filled syringe presentation.
- o Lot-to-lot consistency was defined as meeting criteria that the lower and upper bounds of the 95% CI's for the Geometric Mean Titer (GMT) ratio between vaccine lots fall within the bounds of 0.667 to 1.5.

• Secondary safety endpoints were defined as the proportion of subjects who experienced adverse events. The rate, type, frequency, and severity of AEs in the active treatment arms, for the 3 lots of Afluria multidose presentation, the single lot pre-filled syringe presentation, and the Placebo.

Adverse events were to be monitored after vaccination as follows:

- o Solicited AEs through to Day 4 (Days 0, 1, 2, 3, 4) following vaccination.
- o Unsolicited AEs and SAEs to Exit Evaluation Visit Day 21 following vaccination (acceptable window Day 21-24).
- o AEs were graded according to intensity and relationship to the Study Vaccine**.**

Local reactions and systemic symptoms

Safety and tolerability were reported as the proportion of subjects given vaccine (the multidose presentation, the pre-filled syringe presentation, or Placebo), and who experienced the following solicited local or systemic reactions during the 4 days following vaccination:

Local Reactions

- o Pain
- o Tenderness
- o Erythema/redness
- o Induration/swelling
- o Ecchymosis/bruising

Systemic Reactions

- o Fever
- o Headache
- o Malaise
- o Myalgia
- o Chills
- o Nausea
- o Vomiting

Unsolicited AEs and SAEs were to be coded by the Medical Dictionary for Regulatory Activities (MedDRA) for preferred term and system organ class. The percentage, severity, and relationship to Study Vaccine were presented for each vaccine group according to system organ class and preferred term.

Reviewer comment: Six-month safety data for the collection of SAEs and new onset chronic medical conditions was not requested to be performed in this study. In order to proceed with a priority review of the data contained in an accelerated approval BLA package, collection of these data was not possible. For example, the study ended enrollment in late August 2006, and the collection of six-month safety data would have been completed in late February 2007; this would not have permitted time to lock the study database, complete the safety and immune response analyses, and complete the study reports for submission of a BLA for review in a timely manner for consideration of approval for the 2007-2008 influenza season. Furthermore, this was a product licensed in multiple countries, and postmarketing safety data were available.

8.1.1.1.6 Surveillance/Monitoring

• Please refer to the study design and schedule of procedures in Section 8.1.1.1.2 above. Subjects were directly monitored immediately following vaccination and then returned for re-evaluation on Days 5 and 21 as indicated. Interval history and occurrence of AEs obtained from subjects and diary cards was recorded in the eCRF.
• The "active phase" of the study ended on Day 21. Because of the extensive experience with this product in previous clinical trials and post-marketing experience in Europe and Australia, 6 month safety follow-up data was not collected. There was no active surveillance for influenza infection by culture or other clinical sampling.
• The grading scales for the intensity/severity of local and systemic reactogenicity appear below:

Reactogenicity
Reactogenicity events were those AEs, which were known to occur with this type of vaccine. They were evaluated by utilizing the following grading system:
Table 8.1.1-2

Local Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Pain	Does not interfere with activity	Interferes with activity	Prevents daily activity
Tenderness	Does not interfere with activity	Interferes with activity	Prevents daily activity
Erythema/Redness*	Does not interfere with activity	Interferes with activity	Prevents daily activity
Induration/Swelling*	Does not interfere with activity	Interferes with activity	Prevents daily activity
Ecchymosis/Bruising*	Does not interfere with activity	Interferes with activity	Prevents daily activity

* Was also measured in mm but only functional scale, not size in mm, was used for halting rules

An oral temperature of 37.7°C (100°F) was considered fever in adults. Fever severity was scored as follows:

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Fever	≥37.7°C (100 F) - <38°C (100.4F)	≥38°C (100.4 F) – <39°C (102.2F)	≥39°C (102.2F)

Grading Systemic Events

The following grading system was used to evaluate the subjective systemic events:

Table 8.1.1-3

Local Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Headache	Does not interfere with activity	Interferes with activity	Prevents daily activity
Malaise	Does not interfere with activity	Interferes with activity	Prevents daily activity
Myalgia	Does not interfere with activity	Interferes with activity	Prevents daily activity
Chills	Does not interfere with activity	Interferes with activity	Prevents daily activity
Nausea	Does not interfere with activity	Interferes with activity	Prevents daily activity
Vomiting	Does not interfere with activity	Interferes with activity	Prevents daily activity

• It was the responsibility of the PI/Sub-investigator to ensure that all AEs and other clinically significant findings that occurred were documented and accurately reported and that all site staff understood the requirements related to safety reporting. A DSMB convened by the DMID reviewed the safety information from study subjects. A subset of the DSMB members served as a SMC to review AEs on an ad hoc basis.
• The Investigator was responsible for reporting all AEs that were observed or reported during the study regardless of the relationship to the vaccine. Relationship to Study Vaccine was defined as:

- Associated – The event was temporally related to the administration of the study product and no other etiology explained the event.
- Not Associated – The event was temporally independent of the study product; and/or the event appeared to be explained by another etiology.

• Serious Adverse Events (SAEs)
In accordance with 21CRF 312.32, a SAE was defined as an AE meeting one of the following conditions:

- Results in death during the period of protocol defined surveillance.
- Is life threatening (defined as a subject at immediate risk of death at the time of the event).
- Requires inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance.
- Results in congenital anomaly or birth defect.
- Results in a persistent or significant disability/incapacity.
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

• All SAEs were to be:

- Assessed for intensity and causality by a physician listed on the Form FDA 1572 as the PI/Sub-investigator.
- Recorded on the appropriate SAE report form.
- Followed through to resolution by a study physician.
- Reviewed by the safety monitor, the SMC (periodic review unless associated), DMID, and the IRB.
- Any AE considered serious by the PI/Sub-investigator or that met the aforementioned criteria were to be reported to ---------- (DMID pharmacovigilance contractor), deaths within 24 hours, others within 72 hours, regardless of relationship to the study vaccine.
- All serious, unexpected, and vaccine-related events were to be reported to the FDA within required timelines as specified in 21CRF312.32, 7 days for fatal or life-threatening events, 15 days for all non-fatal non-life-threatening events.

8.1.1.1.7 Statistical considerations for CSLCT-FLU-05-09

• Please see the Statistical Review by Dr. Massie.
• Enrollment was stratified by age: approximately 925 subjects ≥ 18 to < 50 and 325 subjects ≥ 50 to <65 years of age were to be enrolled (total approximately 1250).
• Populations: see above
• Serum HI antibody levels of all subjects was determined in triplicate. Pre- and post-vaccination samples were titrated in triplicate, simultaneously within the same assay. This process was repeated three times on the same day so that the titer assigned to each sample was the geometric mean of three independent determinations.

Reviewer comment: The method of calculating the assigned titer was reviewed with Dr. Massie,

the Statistical Reviewer. The assigned GMT was derived by taking the sum of the natural logs of each independent triplicate observation, dividing that sum by three, and then taking the anti-log of that result. This method reduces the effect of an outlier result on the GMT. $e\left[\frac{\ln(HI1) \times (HI2) \times (HI3)}{3}\right]$

- Co-primary immunogenicity endpoints were:
  - The proportion of subjects with HI titer of at least 1:40
  - The proportion of subjects with an increase in HI antibody titer of at least 4-fold, with a minimum post-vaccination HI titer of 1:40.

  Exact binomial based 95% confidence intervals (CI) were calculated for these rates for each strain. The lower bound of the CIs for the proportion of subjects with HI titer ≥1:40 was to exceed 70% for each strain. The lower bound of the CIs for the proportion of subjects with a 4-fold increase in HI titer was to exceed 40% for each strain.

- To ensure that these results were robust, these analyses were also performed using logistic regression models with lot as a covariate to adjust for potential 'between-lot' differences.

- Secondary immunogenicity endpoints were comparison of the post-vaccination anti-HI antibody GMTs :
  - Between the 3 lots of thimerosal-containing multidose vial presentations;
  - Between the thimerosal-containing multidose vial presentations and the thimerosal-free pre-filled syringe presentation.

  The 95% CIs for these comparisons were to fall within ±0.4055, corresponding to the ratio falling within 0.667 and 1.5.
  Clinical consistency was further investigated by evaluating the co-primary endpoints of proportion with 4-fold increase and of proportion with anti-HI titer ≥1:40 for each of the 3 lots and for the single dose presentation.

- For the Evaluable Population and for each strain and vaccine group the following statistics were calculated using the assigned titer:

  - <u>HI Titers:</u>
    1. The geometric mean of pre-vaccination serum HI titers and 95% CI.
    2. The pre-vaccination number and percentage of evaluable subjects with pre-vaccination serum HI titers ≥ 1:40, and 95% binomial CI.
    3. The geometric mean of post-vaccination serum HI titers and 95% CI.

  - The ratio of the geometric mean increases were reported with 95% confidence limits as follows:

    CSL Vaccine Lot #1/ CSL Vaccine Lot #2
    CSL Vaccine Lot #1/ CSL Vaccine Lot #3
    CSL Vaccine Lot #2/ CSL Vaccine Lot #3
    CSL pre-filled syringe thimerosal-free presentation/ CSL multidose thimerosal-containing vial presentation (all 3 lots)

- Seroconversion rate: the number and percentage of evaluable subjects with serum HI titer < 1:10 pre-vaccination (undetectable) and an increase in serum HI titer to ≥ 1:40 post-vaccination and 95% binomial confidence interval.
- Significant increase: the number and percentage of evaluable subjects with serum HI titer ≥ 1:10 pre-vaccination and a ≥ 4-fold antibody titer increase post-vaccination and 95% binomial confidence interval.
- Seroconversion or significant increase: the number and proportion of subjects achieving seroconversion (pre-vaccination HI titer <1:10 to post HI ≥1: 40) or significant increase in HI titer (pre-vaccination HI titer ≥ 1:10 and post HI / pre HI ≥ 4, or 4-fold increase) was to be reported for each Study Vaccine, along with exact 95% confidence intervals. The lower bounds of these confidence intervals should meet or exceed the corresponding CPMP criteria, namely, 40%.
- Fold increase in HI titers: the geometric mean fold increase in HI titers was to be reported for each Study Vaccine, along with 95% CIs based on a log-normal distribution.

  Reviewer comment: the clinical and statistical reviewers thought that the log normal distribution would be an appropriate evaluation.

- The number and proportion of subjects achieving post-vaccination titers ≥ 1:40 was to be reported for each Study Vaccine, along with exact 95% CIs. The lower bounds of these CIs should meet or exceed the corresponding CPMP criteria, namely 70%.

Reviewer comment: the applicant was notified that consistency of lots would need to be demonstrated before "pooling" of lots in the formal analysis of all subjects who received vaccine.

• Safety Analysis

Safety endpoints and surveillance/monitoring are described above.

Secondary safety endpoints were defined as the proportion of subjects who experienced adverse events. The rate, type, frequency, and severity of AEs for the 3 lots of CSL IVV multidose presentation, CSL IVV pre-filled syringe presentation, and Placebo were calculated along with 95% CIs. Unsolicited AEs were coded by MedDRA version 9.0 for preferred term and system organ class. Summaries classifying events according to severity and relationship to Study Vaccine were presented. For each event type, vaccine and placebo groups were compared using a Fisher exact test without correction for multiple comparisons.

Reviewer comment: The Statistical Reviewer found this to be acceptable.

Subjects with multiple events in the same system organ class and preferred term were counted only once in the subject counts.

• Protocol deviations were reviewed on an ongoing basis and documented prior to unblinding the study.

• Determination of Sample Size

The study was adequately powered to satisfy the primary endpoint for each of the 3

influenza strains. To achieve 80% power overall for all 3 strains, the power per strain had to be at least 92.8% per strain, assuming independence in individuals' immune responses to the 3 strains. The primary objective was achieved if the seroconversion rate and the proportion of subjects with post-vaccination anti-HI titer of ≥1:40 for the active vaccines were significantly greater than the CPMP criteria of 40% and 70% respectively.

If the true seroconversion rate was at least 45.4%, then with a total sample size of N=1000, the power for this comparison exceeds 93% per strain. If the true proportion of subjects with post-vaccination anti-HI titer ≥1:40 was at least 75%, then with a total sample size of N=1000, the power for this comparison exceeds 93% per strain.

Regarding the secondary immunogenicity endpoint of demonstrating consistency across lots and presentations, the applicant calculated that, with an n=250 per arm, an $\alpha = 0.05$ equivalence test using a delta of ±0.4055 (log e of 1.5) has at least 88% power if the standard deviation is 1.4 or less.

Reviewer comment: The Clinical and Statistical Reviewers found the sample size to have adequate power for the primary immune response endpoints.

The sample size for detecting a significant safety event was determined based on the following table (based on Module 5 Vol 1 Sect 9.7.2, p50):

Table 8.1.1-4 Probability of Observing One or More Events for Assumed Event Rates From 0.01% to 5.00%

Sample Size	Assumed Event Rates (%)								
	0.01	0.10	0.33	0.50	1.00	2.00	3.00	4.00	5.00
N=250, a single vaccine group	2.47	22.13	56.60	71.44	91.89	99.36	99.95	99.99	99.99
N=1000, all vaccine groups combined	9.52	63.23	96.45	99.33	99.99	99.99	99.99	99.99	99.99

Source: Final SAP, Version VIII, dated 01 November 2006, Appendix 16.1.9

• Changes in the Planned Analyses

o There were no major changes to the original IND protocol statistical analysis plan other than that local reactogenicity was assessed using a numerical severity scale in addition to the planned qualitative scale.

o There was a post hoc analysis: summary immunogenicity data for the aggregated thimerosal-containing vaccine lots (ie, 1+2+3) were from a post hoc analysis because this analysis was not initially specified due to an unintended omission in the

SAP for the trial. (This is explained in Module 2 Volume 1 Section 2.5 Clinical Overview, p25 of 58.)

8.1.1.2 Results, study CSLCT-FLU-05-09

8.1.1.2.1 Populations enrolled and analyzed

- A total of 1359 subjects were randomized, 1357 received either CSL IVV mulitdose presentation (n = 823), CSL IVV pre-filled syringe (n=266), or thimerosal multidose Placebo (n=268). The first subject enrolled on June 12, 2006, and the last visit for the last subject enrolled was on August 25, 2006. The safety population included all subjects who received CSL IVV (n=1357)
- 1350 subjects (99.5%) completed the study. Of the nine subjects who did not complete the study, 5 were lost to follow-up, 1 withdrew consent, and 2 were randomized but not vaccinated, and one was withdrawn because their data could not be source verified. No subject was withdrawn due to an AE.

Protocol Deviations

- A total of 1357 out of 1359 subjects received the study vaccine and were included in the safety population.

- A total of 1341 subjects were included in the Evaluable Population and 1241 subjects were included in the Per Protocol Population.

- According to the applicant, of the 1357 subjects who received Study Vaccine:
  12 did not provide both a pre and a post-vaccination blood sample
  5 subjects received prohibited oral prednisone. One of these (27FBA106) also lacked pre and post vaccination blood samples for immunogenicity assessments above)
  Total non-evaluable population: 12 + 4 = 16
  Evaluable population: 1357 – 16 = 1341

  101 subjects received an incorrectly stored vaccine
  1 subject was incorrectly randomized
  Total non-per protocol population: 12+4+101+1=118.
  Per Protocol population: 1357 – 118 = 1239.

  The applicant's medical monitor reviewed subjects that received contra-indicated medications post-vaccination and prior to collection of post-vaccination serology. Those subjects whose violations were deemed likely to impact on immunogenicity assessments, eg, use of oral steroids, were excluded from the
  Evaluable population for efficacy analysis prior to unblinding

The following table is based on the applicant's Table 2 Module 5 Volume 1 Section 5.3.1-1, p53. These numbers were confirmed by review of the electronic datasets.

Table 8.1.1-5 Disposition of Subjects CSLCT-FLU-05-09

	CSL Lot 1	CSL Lot 2	CSL Lot 3	CSL L1/2/3	Placebo	CSLpf syringe	Total CSL	Total
#enrolled	273	275	275	823	270	266	1089	1359
#vaccinated	273	275	275	823	268	266	1089	1357
Safety pop	273	275	275	823	268	266	1089	1357
Evaluable pop	270	275	269	814	264	263	1077	1341
Per Protocol	248	255	249	752	244	245	997	1239*
Protocol completed	273	275	272	820	266	264	1084	1350
Protocol terminated	0	0	3	3	4	1	4	8
Unknown	0	0	0	0	0	1	1	1
Reason for Termination								
Serious AE	0	0	0	0	0	0	0	0
Adverse event	0	0	0	0	0	0	0	0
Lost to f/u	0	0	3	3	1	1	4	5
Protocol deviation	0	0	0	0	0	0	0	0
Withdrawal by subject	0	0	0	0	1	0	0	1
Withdrawal by investigator	0	0	0	0	0	0	0	0
Death	0	0	0	0	0	0	0	0
Randomized but Not vaccinated	0	0	0	0	2	0	0	2

Pf = pre-filled syringe

Reviewer comment: There were very few subjects who withdrew (n=1, placebo group) or who were lost to follow-up (n=5, four CSL IVV, one Placebo recipient). The four CSL IVV recipients for whom the protocol was terminated were terminated because they were lost to follow-up.

Review of the electronic datasets also revealed a non per protocol population of n=118. Eight of these were terminated as noted above. 101 were from the Vanderbilt site. Of these 101 Vanderbilt subjects, one (27FVD075) was also lost to follow-up and terminated. Five subjects received prednisone and were thus excluded from the per protocol populations. This was confirmed by review of the electronic datasets and line listings.

*Reviewer comment: There is a discrepancy between the applicant's CSR text which reports the Per Protocol population as being 1239 and the applicant's tables which list the Per Protocol population as 1241. The reviewer believes that the calculation of 1239 is correct, and that the

applicant's tables were likely tables based on "all randomized subjects" without taking into account the 2 subjects who were randomized but never vaccinated.

The 101 Vanderbilt recipients received vaccine that "may have been frozen for an indeterminate but short period prior to vaccination". To better assess the impact, if any, of this improper storage on the immunogenicity results, FDA requested that the applicant provide immunogenicity analyses on both the evaluable and the per protocol populations, or, alternatively, to run the analyses on this subset of Vanderbilt subjects. These results are presented in Section 8.1.1.2.2. of this BLA review.

Review of the electronic datasets revealed the distribution of treatment vaccine among these Vanderbilt subjects as follows:

Table 8.1.1-6 101 CSL IVV recipients of improperly stored vaccine at the Vanderbilt site by treatment allocation (generated by reviewer)

	CSLmd Lot 1	CSLmd Lot 2	CSLmd Lot3	Placebo	CSLpf Syringe	Total
# of subjects	22	20	19	20	20*	101

md = multidose vial
pf = pre-filled syringe

*One of the CSL pre-filled syringe subjects was terminated, lost to follow-up.

Reviewer comment: an FDA inspection of the clinical trial facility confirmed the improper storage of vaccine. BIMO conducted inspections of three of the clinical study sites representing 28% of the total subjects enrolled in this study, verified the improper storage of vaccine at the Vanderbilt site, and found deficiencies in documenting the storage temperature of the study vaccines at both the Vanderbilt and Stanford sites. However, in consultation with BIMO, it is unlikely that the protocol deviations had a significant impact on the data or compromised the integrity of the study.

The following table is based on Table 3 Module 5 Volume 1 Section 5.3.5.1-1, p 58, and confirmed by review of the electronic datasets:

Table 8.1.1-7 Demographics (Evaluable Population) Pivotal Study CSLCT-FLU-05-09

Evaluable population		CSLmd Lot 1 N=270	CSLmd Lot 2 N=275	CSLmd Lot 3 N=269	Placebo N=264	CSLpf Syringe N=263	All CSL N=1077
Character-istic	Parameter or category	Value or N(%)	Value or N(%)	Value or N(%)	Value or N(%)	Value or N(%)	Value or N(%)
Age (years)*	Mean	37.88	38.85	37.36	38.09	38.15	
Gender	Male	93 (34.4)	103 (37.5)	105 (39.0)	87 (33.0)	103 (39.2)	404 (37.5)

	Female	177 (65.6)	172 (62.5)	164 (61.0)	177 (67.0)	160 (60.8)	673 (62.5)
Race	Native Indian/ Alaskan	3	4	2	4	1	10
	Asian	12	14	23	15	19	68
	Native Hawaiian	0	1	1	1	0	2
	African American	28	36	35	30	33	132
	Caucasian	229	221	210	216	214	874
	Unknown						

*Mean ages calculated by the Statistical Reviewer and based on the Safety population rather than the Evaluable population, but the difference between these populations is small and the numbers are therefore included in this table which is otherwise based on the Evaluable population.

Reviewer comment: the demographic data in the electronic datasets were identical to the applicant's results. The mean age of subjects was comparable between the individual CSL IVV groups and placebo. The overall mean age for the CSL groups was 38.1 years and for the placebo group 38.3 years. The majority of subjects were female, 62.5% for the CSL IVV recipients and 67.0% for the placebo group. The majority of subjects were Caucasian, >80.0% in all groups. The safety population demonstrated similar demographic characteristics.

Table 8.1.1-8 Enrollment by Study Center
(based on review of electronic datasets)

Study center	CSL IVV	Placebo	Total
St Louis U	168	42	210
Cincinnati	140	34	174
U. Rochester	127	32	159
U. Maryland	137	34	171
Baylor	89	22	111
U. Iowa	121	30	151
Vanderbilt	127	33	160
Duke	73	17	90
Stanford	107	26	133
Total	1089	270	1359

Reviewer comment: although there were relatively fewer subjects at the Duke and Baylor sites, enrollment was generally equally distributed.

Table 8.1.1-9 Study Day that subjects received the "Day 21" study visit blood draw
(generated from review of the datasets)

Day	CSLmd Lot 1 N, (%)	CSLmd Lot 2 N, (%)	CSLmd Lot 3 N, (%)	Placebo N, (%)	CSLpf Syringe N, (%)
20	5, 1.8	0, 0	2, 0.7	3, 1.1	3, 1.1
21	182, **66.7**	190, **69.1**	186, **67.6**	184, **68.4**	182, **68.4**
22	45, 16.5	36, 13.1	36, 13.1	28, 10.4	33, 12.4
23	11, 4.0	15, 5.5	11, 4.0	16, 5.9	10, 3.8
24	18, 6.6	20, 7.3	18, 6.5	20, 7.4	23, 8.6
25	2, 0.7	4, 1.5	4, 1.5	3, 1.1	7, 2.6

Reviewer comment: the majority of subjects in all treatment groups had post-vaccination HI antibody titers drawn on study Day 21, and nearly all had post-vaccination titers drawn by Day 25.

Influenza History

There was no information relative to previous history of influenza illness provided in the datasets. Review of concomitant medications in the electronic dataset revealed no subject with recent influenza vaccination.

Line listings from the paper submission were reviewed and confirmed the applicant's report that approximately half of all CSL vaccine recipients and 46.6% of placebo recipients had a previous history of influenza illness. The following table is based on the applicant's Module 5 Volume 2 Appendix 16.2.4 and on Table 13 Module 5 Volume 1 Section 5.3.1-1, p96.

Table 8.1.1-10 Previous Vaccination against Influenza CSLCT-FLU-05-09

	CSLmd Lots 1/2/3 N=823	CSLpf Syringe N = 266	All CSL Vaccines N = 1089	Placebo N=268

Previous Influenza Vaccination N (%)				
2002-2003	323 (32.9)	93 (35.0)	416 (38.2)	101 (37.7)
2003-2004	346 (42.0)	111 (41.7)	457 (42.0)	108 (40.3)
2004-2005	326 (39.6)	110 (41.4)	436 (40.0)	96 (35.8)
2005-2006	392 (47.6)	120 (45.1)	512 (47.0)	114 (42.5)
Dec 2005	17 (2.1)	4 (1.5)	21 (1.9)	5 (1.9)
Jan 2006	4 (0.5)	1 (0.4)	5 (0.5)	0
Feb-Apr 2006	0	0	0	0

Reviewer comment: a similar proportion of CSL vaccine recipients reported receiving influenza vaccine in the four years prior to receiving study vaccine as compared with placebo. Few subjects received influenza vaccine in the 6 months prior to vaccination with study vaccine consistent with exclusion criteria. The following table shows that those who received seasonal influenza vaccine as late as January 2006 were not vaccinated with study vaccine until approximately 6 months later. Review of the datasets revealed that no subjects had received influenza vaccine after January 2006:

Table 8.1.1-11 Date of Study Vaccine for Subjects who had Most Recently Received Seasonal Influenza Vaccine Prior to Study CSLCT-FLU-05-09

Subject ID	Date of Previous Influenza vaccine	Date of Study Vaccine
27FBA013	January 2006	July 7, 2006
27FSL213	January 2006	July 11, 2006
27FST038	January 2006	June 26, 2006
27FST151	January 2006	July 21, 2006
27FST158	January 2006	July 24, 2006

Immunogenicity Evaluation

Data Sets Analyzed

- Evaluable Population, n=1341
  - The set of all subjects vaccinated with Study Vaccine on Day 0 and who provided both pre- and post-vaccination blood samples
  - Used for all immunogenicity summaries and analyses
  - Immunogenicity results could be excluded from the analysis if any of the following occurred during the study: use of any investigational product; use of immunosuppressive/immunomodulative medication; administration of any other vaccine, immunoglobulins, or blood products during the study; diagnosis of immunodeficiency condition
- Safety Population, n=1357
  - The set of subjects used for the analysis of safety data

- All subjects who received a dose of Study Vaccine on Day 0
- Two of the original 1359 enrollees were randomized but did not receive study vaccine on Day 0 and were subsequently excluded

• Per Protocol Population, n=1241

- Consisted of all subjects in the Evaluable Population who did not experience any significant protocol deviations which were thought to potentially have an effect on the immunogenicity assessments. This population was not used for the original immunogenicity analysis, but these analyses were subsequently performed at the request of FDA.

Demographic Characteristics CSLCT-FLU-05-09

For the Evaluable population, the mean ages of the CSL IVV and Placebo groups were 38.1 and 38.3 years respectively. A slight majority of subjects were female, and the majority were Caucasian across all groups. The Safety population had similar demographics. The following table was reproduced from the applicant's Table 3 Module 5 Volume 1 Section 5.3.5.1-1, p58, and confirmed by review of the electronic datasets.

Table 8.1.1-12 Demographic Characteristics CSLCT-FLU-05-09

Evaluable Pop	CSL multidose	CSL prefilled Syringe	Placebo	Total
Characteristic	n = 814	n = 263	n = 264	n = 1341
Age Mean	38.0	38.1	38.3	38.1
%Gender Male	37.0	39.2	33	37.5
Female	63	60.8	67	62.5
%Race Caucasian	81.1	81.4	81.8	81.2
Black	12.2	12.5	11.4	12.3
Asian	6.0	7.2	5.7	6.3
Other/unknown	2.8	0.4	3.0	2.2

Reviewer comment: demographic characteristics appear to be generally representative of the U.S., population with the exception of persons of Hispanic/Latino origin.

Influenza History

For the Safety Population, 54% of CSL vaccine recipients and 46.6% of placebo recipients had a history of influenza illness. Previous vaccination with influenza vaccine from 2002 to 2006 was comparable among all groups (see Table above). Previous adverse reaction to influenza vaccine was low in all groups, 1.1 to 3.7%.

General Medical History and Concomitant Medications

The applicant reports that no subjects had a significant pre-existing or current medical condition which was felt to interfere with their participation in the study. The following table was generated from review of the electronic datasets, and displays the absolute number and percent of subjects with various past medical conditions.

Table 8.1.1-13 General Medical History CSLCT-FLU-05-09

Medical condition	CSL * n=1080, %	Placebo n=270, %
Ears,nose,throat	589 (54.5)	141 (52.2)
Cardiovascular	190 (17.6)	46 (17.0)
Respiratory	102 (9.4)	27 (10.0)
Gastrointestinal	195 (18.0)	42 (15.6)
Urology	67 (6.2)	17 (6.3)
Neurology	109 (10.0)	24 (8.9)
Hematology	38 (3.5)	10 (3.7)
Endocrinology	75 (6.9)	25 (9.3)
Musculoskeletal	343 (31.8)	98 (36.3)
Genital/reproductive	353 (32.7)	95 (35.2)
Dermatologic	167 (15.4)	52 (19.3)
Allergy	554 (51.3)	132 (48.9)
Oncology	35 (3.2)	6 (2.2)
Immunodeficiency	0	0
Psychiatric	133 (12.3)	44 (16.3)
Drugs/alcohol	19 (1.8)	7 (2.6)
Autoimmune disease	4 (0.4)	3 (1.1)
Other	178 (16.5)	36 (13.3)

*CSL= all four treatment groups, multidose vials and pre-filled syringe

Reviewer comment: The electronic datasets for subjects with a history of cancer were reviewed. The cancers included remote breast, cervical, testicular, and thyroid cancer, and many subjects with basal cell skin cancer. None were receiving immunosuppressive medications. The electronic datasets for subjects with a history of autoimmune disease were also evaluated for immunosuppressive medications:

Table 8.1.1-14 Subjects with Autoimmune Disease CSLCT-FLU-05-09

Subject ID	Vaccine	Disease	Immunosuppressive medication
27FCI087	Placebo	Rheumatoid vs Osteoarthritis	No
27FDU018	Placebo	Alopecia areata 1990 Resolved	No
27FSL164	Placebo	Vitiligo 1972	No
27FST064	CSL	Grave's disease 5/2005	No
27FUM108	CSL	Sjogren's syndrome	No
27FUR008	CSL	ANA connective tissue disease	No
27FVD043	CSL	Lichen Planus 2005	No

Reviewer Comment: Five subjects took prohibited systemic corticosteroids during the study and were appropriately excluded from the Evaluable and Per Protocol populations prior to unblinding. The exception to this was Subject 27FST164, a 24 year old female who was vaccinated with placebo on August 1, 2006. On August 18, 2006, she received dexamethasone and hormonal treatment in preparation for ovarian egg harvest. She was excluded from the Evaluable Population, and therefore the immunogenicity analysis, but remained in the Per Protocol population. This should not have significantly affected the immunogenicity results.

Table 8.1.1-15 Prohibited Medications CSTCT-FLU-05-09

Patient ID	Medication	Tx group	Evaluable pop	Per Protocol
27FBA106	Prednisone	CSLmd Lot 1	No	No
27FDU085	Prednisone	CSLpf syringe	No	No
27FSL030	Prednisone	CSLmd Lot 1	No	No
27FVD041	Prednisone	CSLpf syringe	No	No
27FST164	Dexamethasone	Placebo	No	Yes

No subject received prohibited influenza vaccine during the study. One subject 27FSL098 (CSL multidose vial Lot #1) received tetanus and diphtheria vaccine, and another subject 27FST033 (CSL prefilled syringe) received tetanus toxoid, but were not excluded from the Evaluable or Per Protocol populations.

Table 8.1.1-16 Subjects Who Received other Vaccines During the Study

Patient ID	Medication	Date of Med	Indication	Tx group	Date of Study Vaccine	Evaluable Pop/ Per protocol
27FSL098	Tetanus/ Diphtheria vaccine	07/12/06	Puncture Wound	CSLmd Lot #1	06/21/06	Yes/yes
27FST033	Tetanus toxoid	07/09/06	Embedded splinter	CSLpf syringe	06/27/06	Yes/yes

Reviewer comment: these protocol violations appear to be in very small numbers and are unlikely to have a strong impact on the overall safety and immune response results.

8.1.1.2.2 Efficacy endpoints and outcomes, summary of applicant's analyses:

The immunogenicity analyses were performed on the Evaluable Population, n=1341, total CSL

IVV recipients = 1077, Placebo = 264.

The prospective co-primary endpoints were:

- The proportion of subjects with a minimum post-vaccination titer of ≥ 1:40. The lower bound of the 95% CI was to exceed 70% for each strain.
- The proportion of subjects with an increase in HI antibody titer of at least 4-fold, with a minimum post-vaccination HI titer of 1:40. The lower bound of the 95% CI was to exceed 40% for each strain.

The following table was reproduced from the applicant's data tables located in Module 5, Volume 1, Section 5.3.5.1-1, p63, and Section 14.2, p170.

Table 8.1.1-17 Co-primary Endpoints: proportion with 4-fold increase in HI titer to at least 1:40 and proportion with post-vaccination HI titer ≥1:40 (Evaluable Population) CSLCT-FLU-05-09

Strain	4-fold increase in HItiter			Post-vaccination proportion with HI titer ≥1:40.	
		Overall[1]. n=1077	Placebo n=264	Overall[1] n=1077	Placebo n=264
H1N1 % 95% CI (%)	48.7 **45.6**, 51.7%	2.3 0.8, 4.9%	97.8 **96.7**, 98.6%	74.6 68.9, 79.8%	
H3N2 % 95% CI(%)	71.5 **68.7**, 74.2%	0	99.9 **99.5**, 100.0%	72.0 66.1, 77.3%	
B strain % 95% CI(%)	69.7 **66.9**, 72.5%	0.4 <0.1, 2.1%	94.2 **92.7**, 95.6%	47.0 40.8, 53.2%	

[1]Overall group includes CSL lots 1, 2, and 3, and CSL prefilled syringe

Following vaccination, the lower bounds of the 2-sided 95% confidence intervals for the proportion with a four-fold increase in HI antibody titer to at least 1:40 were: 45.6% for H1N1, 68.7% for H3N2, and 66.9% for the B/Malaysia strain.

The lower bounds of the 2-sided 95% CI for the proportion of subjects whose post-vaccination HI titer was ≥1:40 was 96.7% for H1N1, 99.5% for H3N2, and 92.7% for B/Malaysia.

The lower bound of the 2-sided 95% CIs exceeded the predefined criteria specified in the Statistical Analysis Plan for both co-primary endpoints. No significant increase in post-vaccination HI titers was seen in the Placebo group.

Reviewer comment: the fact that the recipients of placebo did not demonstrate immune responses indicates that the immune response results among recipients of vaccine were indeed due to an immune response to the vaccine and not due to circulating influenza.

The secondary immunogenicity endpoints were:

- Comparison of Geometric Mean Titers (GMT) to influenza Hemagglutinin antigens after vaccination of the active treatment arms: between each of the 3 lots of Afluria multidose vials and between each of the 3 lots of Afluria multidose vials and the pre-filled syringe presentation.
- Demonstration of lot-to-lot consistency was shown by meeting criteria that the lower and upper bounds of the 95% CI's for the Geometric Mean Titer (GMT) ratio between vaccine lots falls within the bounds of 0.667 to 1.5.

The following table was generated from the sponsor's data (Table 19, Module 5, Volume 1, Section 14, p176):

Table 8.1.1-18 Post-vaccination GMTs, Lot-to-Lot Consistency (Evaluable Population, CSLCT-FLU-05-09)

Strain	Comparison	Ratio	95% CI
H1N1	CSL lot 1/2	1.092	(0.933, 1.278)
	CSL lot 1/3	1.017	(0.868, 1.191)
	CSL lot 2/3	0.931	(0.795, 1.090)
	CSL pf syringe/CSL md vial	1.020	(0.895, 1.164)
H3N2	CSL lot 1/2	0.839	(0.700, 1.005)
	CSL lot 1/3	0.929	(0.775, 1.114)
	CSL lot 2/3	1.107	(0.924, 1.327)
	CSL pf syringe/CSL md vial	1.039	(0.897, 1.203)

B Strain	CSL lot 1/2	1.167	(0.966, 1.410)
	CSL lot 1/3	1.058	(0.875, 1.280)
	CSL lot 2/3	0.907	(0.750, 1.096)
	CSL pf syringe/CSL md vial	1.065	(0.911, 1.243)

CSL lot 1/2/3 = CSL IVV multidose presentation (with thimerosal) Lot #1/2/3.
CSL pf syringe = CSL IVV pre-filled syringe presentation (no thimerosal).
CSL md vial = combination of the 3 CSL IVV multidose vial titers from the 3 lots.

Reviewer comment: There were no significant differences between the 3 CSL IVV multi-dose lot presentations or between those lots and the single lot pre-filled syringe presentation. Criteria for lot-to-lot consistency was fulfilled, and it was, therefore, appropriate to "pool" the immune response data from all four of the groups that received CSL vaccine.

- **Per Protocol Population**

FDA requested an immunogenicity analysis on the Per Protocol population which excluded the 101 subjects at the Vanderbilt site whose vaccine had been stored improperly. The following table was reproduced from applicant's response to FDA request, 125254/0 Login ID 417391, amendment to the BLA, vol 1, attachment 9:

Table 8.1.1-19 Co-primary endpoints, Per Protocol Population: proportion with 4-fold increase in HI antibody titer (minimum 1:40) and proportion with post-vaccination anti-HI antibody ≥ 1:40, CSLCT-FLU-05-09

Strain	4-fold increase in HI titer Overall[1] n = 997	Proportion with post-vaccination HI titer ≥ 1:40 Overall[1] n = 997
H1N1 % 95% CI (%)	**50.2** 47.0, 53.3	**97.8** 96.7, 98.6
H3N2 % 95% CI (%)	**72.3** 69.4, 75.1	**100.0** 99.6, 100.0
B Strain % 95% CI (%)	**70.5** 67.6, 73.3	**94.6** 93.0, 95.9

[1]Overall includes CSL Lots 1, 2, and 3, and CSL pre-filled syringe.

Reviewer comment: the results of the Per Protocol point estimates were verified by evaluation of the electronic datasets. The proportion with 4-fold increase in HI titer and proportion with HI titer ≥1:40 in the Per Protocol population were comparable to that found in the Evaluable Population. The applicant did not feel that the Evaluable Population differed significantly from the Per Protocol Population, and, therefore, did not feel that repeat immunogenicity analyses on the Per Protocol Population were necessary.

The Statistical Reviewer provided the following tables displaying the co-primary endpoints for each vaccine strain and based on the Per Protocol population:

Table 8.1.1-20 SeroProtection Rate Based on Per Protocol Proportion of Subjects with ≥1:40 Titer Post-vaccination of Immunogenicity Response of HI (with 95% CI in parenthesis)

Strain	Treatment Group					
		Placebo **(n=264)**	Lot #1 **(n=270)**	Lot #2 **(n=275)**	Lot #3 **(n=269)**	Single dose **(n=263)**
H1N1	76.2% (68.9-79.8)	96.7% (93.8-98.5)	98.2% (95.8-99.4)	97.4% (94.7-98.8)	98.9% 96.7-99.8)	
H3N1	72.0% (66.1-77.3)	100.0% (98.6-100.0)	99.6% (98.6-100.0)	100.0% (98.6-100.0)	100.0% (98.6-100.0)	
B Strain	47.0% (40.8-53.2)	95.4% (92.2-97.7)	93.3% (90.3-96.4)	92.3% (89.2-95.7)	93.9% (91.2-97.1)	

Table 8.1.1-21 SeroConversion Rate Based on Per Protocol Proportion of Subjects with ≥1:40 Titer Post-vaccination of Immunogenicity Response of HI (with 95% CI in parenthesis)

Strain	Treatment Group					
		Placebo **(n=264)**	Lot #1 **(n=270)**	Lot #2 **(n=275)**	Lot #3 **(n=269)**	Single dose **(n=263)**
H1N1	1.7% (0.8-4.9)	48.5% (42.4-54.7)	48.4% (42.3-54.4)	49.1% (42.9-55.2)	48.7% (42.5-54.9)	
H3N1	0.0% n/a	69.3% (63.4-74.7)	71.3% (65.5-76.5)	75.5 (69.9-80.5)	70.0% (64.0-75.4)	
B Strain	0.4% (0.0-2.1)	71.8% (66.1-77.1)	66.7% (62.1-73.5)	68.4% (63.3-7406)	68.4% (64.0-75.4)	

Reviewer comment: the Statistical Reviewer's lower bound results for the individual lots and presentations are only slightly lower than the applicant's results which combined all four CSL IVV groups. This difference appears to be acceptable.
In addition, the Statistical Reviewer performed a sensitivity analysis using the lowest of the triplicate HI titers rather than the GMT to calculate the endpoints. While these results were also lower than the applicant's, they met FDA criteria for immune response, and the immune response results were considered robust. Please refer to the Statistical Review for further discussion of these results.

- **Subgroup Analysis:**

The Statistical Reviewer provided the following immunogenicity analyses by site:

Table 8.1.1-22 CSLCT-FLU-05-09 Proportion with 4-fold increase in HI titer by study site

Center	Strain		Treatment				
			Placebo	Lot #1	Lot #2	Lot #3	Syringe
Baylor	**B St**	.	81.8	82.6	85		72.7
		H1N1	4.5	63.6	69.6	60	63.6
		H3N2	.	81.8	87	100	72.7
Cincinnat	**B St**	.	61.8	66.7	63.6		58.8
		H1N1	2.9	47.1	44.4	39.4	38.2
		H3N2	.	61.8	83.3	72.7	70.6
Duke	**B St**	.	73.7	73.7	66.7		82.4
		H1N1	6.3	52.6	42.1	61.1	52.9
		H3N2	.	63.2	84.2	88.9	64.7
St. Louis	**B St**	.	76.2	73.8	76.2		78.6
	65.6	63.3					

H1N1	. Collection of SAEs (Day 0 - Exit Evaluation)	21.9	31.3	37.5	50

H3N2	.	59.4		53.1	75	56.7 Nasal swab for intercurrent flu-like illness*	Review of concomitant medication

Table 8.1.1-23 CSLCT-FLU-05-09 Proportion with post-vaccination HI titer ≥1:40 by study site

*If applicable

Center	Strain	Treatment				
		Placebo	Lot #1	Lot #2	Lot #3	Syringe
Baylor	**B St**	40.9	95.5	91.3	100.0	100.0
	H1N1	72.7	95.5	95.7	100.0	100.0
	H3N2	63.6	100.0	100.0	100.0	100.0
Cincinnat	**B St**	44.1	97.1	88.9	90.9	88.2
	H1N1	79.4	97.1	97.2	97.0	100.0
	H3N2	73.5	100.0	100.0	100.0	100.0
Duke	**B St**	75.0	89.5	100.0	83.3	100.0
	H1N1	93.8	94.7	100.0	94.4	100.0
	H3N2	75.0	100.0	100.0	100.0	100.0
St. Louis	**B St**	46.3	97.6	92.9	97.6	97.6
	H1N1	68.3	90.5	100.0	100.0	97.6
	H3N2	75.6	100.0	100.0	100.0	100.0
Stanford	**B St**	46.2	100.0	88.9	100.0	96.2
	H1N1	65.4	100.0	92.6	96.2	100.0
	H3N2	69.2	100.0	100.0	100.0	100.0
U. Iowa	**B St**	50.0	96.7	100.0	84.4	89.7
	H1N1	75.0	93.3	100.0	96.9	96.6
	H3N2	71.4	100.0	100.0	100.0	100.0
U. Maryla	**B St**	48.5	97.1	97.1	97.1	100.0
	H1N1	63.6	100.0	100.0	100.0	100.0
	H3N2	72.7	100.0	100.0	100.0	100.0
U. Roches	**B St**	38.7	93.8	90.3	93.8	93.5
	H1N1	87.1	100.0	96.8	93.8	100.0
	H3N2	67.7	100.0	100.0	100.0	100.0
Vanderbil	**B St**	45.5	90.6	96.9	87.5	90.0

H1N1	75.8	100.0	100.0	96.9	96.7
H3N2	75.8	100.0	96.9	100.0	100.0

Reviewer comment: The proportion with a four-fold increase in post-vaccination HI antibody titers in the Vanderbilt subjects was lower for the H1N1 strain, multi-dose vials, as compared to subjects at other sites. While it is possible that the improper freezing of the vaccine prior to administration affected the immune response, the proportion of subjects from this site with post-vaccination H1N1 HI antibody titers ≥1:40 ranged from 96.7 to 100.0, and it is also possible that the low four-fold increase rate was related to other factors such as high pre-vaccination titers. Regardless of the explanation for the relatively lower response to the H1N1 strain among the Vanderbilt subjects, the immunogenicity results for subjects from this site do not appear to have affected the overall immunogenicity results of the Evaluable Population when compared to the Per Protocol Population (which excluded the 101 Vanderbilt subjects). Because the immunogenicity results between these two populations are so similar, the decision by the applicant to use the Evaluable Population for the immunogenicity analyses appears acceptable. Please refer to Dr. Tammy Massie's Statistical Review for additional comments on this analysis.

H1N1 Reviewer comment: According to the EMEA guidance document, at least one of the above criteria should be met for each influenza antigen. The assessments were based on point estimates rather than the lower bound of the 95% confidence interval.

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45.2 Reviewer comment: the criteria for demonstration of non-inferiority of immune responses were not pre-specified in the protocol. o The effect of baseline population factors on immune responses were assessed via multiple linear regression of post-vaccination log titers versus pre-vaccination log titers, vaccination history, age, and sex. The post-vaccination immune response rates were assessed via logistic regression models. Sub-group analyses were performed for sub-populations with similar vaccination histories, pre-vaccination titers, or by age groups. A formal comparison between the immunogenicity results of CSL IVV and Influsplit was not planned. However, summaries of immune responses were presented.

o To assess the immune response of CSL IVV according to the criteria of the *CPMP/BWP/214/96 Note for Guidance on Harmonization of Requirements for Influenza Vaccines* for Older Adults, which for participants > 60 years of age were as follows:

The proportion of subjects with an increase in HI antibody titer of at least 4-fold with a minimum post-vaccination HI titer of 1:40 should be > 30%.

The mean geometric increase should be > 2.0;

The proportion of participants achieving a HI titer ≥ 1:40 should be >60%.

59.5 • **Safety endpoints:**

57.1 o The assessment of the frequency of Solicited systemic and local reactions and Unsolicited adverse events (AEs)

57.1 Frequency of Solicited local reactions for 5 days following vaccinaton (Day 0 to Day 4): pain, tenderness, erythema, swelling, induration and ecchymosis at the vaccination site. Compared to Influsplit.

H3N2 Frequency of SAEs occurring during the study period (21 + 4 days post-

vaccination).

Frequency of Solicited general symptoms for 5 days following vaccination: fever, headache, malaise, myalgia, chills, nausea, and vomiting. Compared to Influsplit.

Frequency of Unsolicited AEs for 21 + 4 days following vaccination. Compared to Influsplit.

• **Co-primary immunogenicity endpoints:**

o The number and percentage of evaluable participants with a minimum post-vaccination HI titer of 1:40.

o Seroconversion or the number and percentage of evaluable participants with an increase in HI antibody titer of at least 4-fold and with a minimum post-vaccination HI titer of 1:40.

o For each strain, the proportion of study participants achieving seroconversion should be significantly > 30% and the proportion achieving HI titers ≥ 1:40 should be significantly > 60% as assessed by 97.5% one-sided binomial confidence intervals.

• **Secondary immunogenicity endpoints:**

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61.9 **8.1.2.1.6 Surveillance/Monitoring**
69

69 • Please refer to the schedule of procedures below (from the clinical study report):

73.8

Stanford PROCEDURE	**B St STAGE**	.		77.8	51.9
	73.1	**H1N1 (DAY 0) VISIT 1**	3.8 **DAY 8 (±2 days)**	40.7 **EXIT EVALUATION** 48.1 **(DAY 21 + 4)**	**PRE-STUDY**
46.2 Invitation to participate	**H3N2**	.			
55.6 Informed consent procedure	76.9	50		**U. Iowa**	

. Medical history including; 70 • History of Influenza 63.3 • History of previous Influenza Vaccination 56.3 75.9 **H1N1**	.	56.7	40	46.9
H3N2	.	70	Brief Medical Evaluation	
68.8 Physical examination	72.4	**U. Maryla**	**B St** (if clinically indicated)	(if clinically indicated)
73.5 Temperature recorded	77.1	79.4	82.4	

H1N1 Pre-vaccination serology sample obtained	6.1	61.8	54.3	52.9
H3N2	.	79.4	Review of Inclusion/Exclusion criteria	
79.4 Administration of Study Vaccine	79.4	**U. Roches**	**B St**	

81.3 Diary card completed by participants (Day 0-4) including Temperature	61.3	62.5	48.4	
H1N1 Diary card mailed to Study Site	.	53.1	45.2	46.9

H3N2	.	84.4	5-day Solicited Adverse Event Diary Card review	
65.6 21-day Unsolicited Adverse Event Dairy Card review	77.4	**Vanderbil**	**B St** (Adverse Events assessment only)	

56.3 Post vaccination serology sample obtained	62.5	60	60	Total vaccinated
60 (100%)	Safety population	60 (100%)	60 (100%)	
Evaluable population	59 (98.3%)	60 (100%)	Protocol completed	
60 (100%)				

69.2
46.2
66.7
B St
48.3
73.3
.
44.1
68.6
3.2

38.7

74.2

.

• **Unplanned or interim analyses**
The applicant stated that there were no efficacy endpoints not prospectively stated in the trial. There were no unplanned or interim analyses.

• **Dropouts**
The applicant stated that there were no replacements for dropouts or missing data.

• **Multiplicity**
The applicant reported that the study was adequately powered to satisfy the primary endpoints for each strain, and that adjustments were made for multiple comparisons of the secondary endpoints. Pre-GMT titers were used as co-variates to avoid confounding of results by subjects whose pre-vaccination titers were already ≥1:40. Please refer to Dr Massie's Statistical Review for further discussion of this point.

• **Covariate analyses/adjustments**

The applicant reports that in the analysis of post-vaccination titers, pre-vaccination titers, vaccination history, age (18 to ≤49 years and 50 to ≤65 years) and gender served as co-variates. Lot served as covariate in the logistic regression analysis of the primary endpoints, i.e., the secondary endpoint comparision of the GMT ratios between lots and across presentations.

Reviewer comment: The applicant states that the above covariate analyses were undertaken (Module 5 Volume 1 Section 5.3.5.1-1 p71) and provides results in Tables 19 and 25 (Module 5 Volume 1 Section14 pp176 and 183), but does not discuss these results, for example, how the covariates influenced the endpoints, in the text. Please refer to Dr Massie's review for further discussion.

• **Immunogenicity Conclusions CSLCT-FLU-05-09**

o Vaccination with CSL Influenza Vaccine (CSL IVV), both the multidose (thimerosal-containing) and the pre-filled syringe (thimerosal-free) presentations, produces an immune response for which the lower bounds of the two-sided 95% confidence interval exceeds the co-primary immunogenicity criteria of: 1) proportion with a four-fold increase in HI titer to at least 1:40 exceeds 40% and 2) proportion of subjects with a post-vaccination HI titer ≥ 1:40 exceeds 70% for all three vaccine antigen strains.

o Lot-to-lot consistency was demonstrated between the CSL IVV multidose vial (thimerosal-containing) presentations (Lots 1, 2, and 3) and the CSL IVV pre-filled syringe (thimerosal-free) presentation. Comparable GMT ratios between lots implied that the four vaccine treatment groups and the two different presentations

used in the pivotal study elicited similar immune responses.

8.1.1.2.3 Safety outcomes

The Safety Population was comprised of all 1357 subjects who received a single injection of Study Vaccine. 823 subjects received CSL IVV multidose vial presentation (lots 1, 2, and 3), 266 received CSL IVV pre-filled syringe presentation, and 268 received Placebo.

The sponsor used Fisher's exact test to determine significant differences between subjects who received CSL IVV versus Placebo. The Statistical Reviewer concurred with this analytic approach.

Reviewer comment: the Safety review was conducted from the source or electronic datasets, and will be descriptive in nature.

• **Serious Adverse Events (SAEs)**

There was only one SAE reported by the sponsor during this study. The CRF and SAE report forms were reviewed. Subject 27FCI154, a 42 year old female, received CSL IVV multidose vial Lot 1 on July 11, 2006. On July 22, 2006, the subject was the victim on an assault, suffered a fracture of the right femur, and,was hospitalized. She received a tetanus shot on July 23, 2006, and underwent internal fixation of the femur. She was discharged on July 25, 2006 and was subsequently lost to follow-up. This SAE was felt not to be associated with the study vaccine.

There were no other SAEs or deaths in either the pivotal study or in the five other supporting studies to the BLA. There were, however, two other events of special interest which occurred in study CSLCT-NHF-05-09:

- Subject 27FVD137 Serum sickness - a 32 year old male was vaccinated with CSL thimerosal-containing multidose vial vaccine Lot 3 on July 14, 2006. He had received influenza vaccine for the previous four years. On Day 1 post-vaccination, the subject developed erythematous papules on exposed areas of skin which over the ensuing weeks evolved into an allergic type reaction consisting of hives, urticaria, dermatographism and arthralgias, "moderate" in severity. He was treated with oral anti-histamines, was referred to an allergist, and on September 15, 2006, was begun on oral prednisone. Symptoms recurred with steroid taper, but responded to a second course of steroids. Follow up in January and April 2007 revealed persistent dermatographism and skin reactivity which precluded allergy skin testing with Flumist. The subject also continued to experience occasional urticaria which were treated with oral anti-histamines as needed. The outcome of this event was recorded as "resolved with sequelae" and the event was considered to be "associated" with the study vaccine.

- Subject 27FVD153 Pregnancy - a 27 year old female was vaccinated with CSL

thimerosal-containing multidose vial vaccine Lot 3 on July 26, 2006. Urine pregnancy test on the day of vaccination was negative, but both urine and serum pregnancy tests were positive on Visit 3 Day 21, August 16, 2006. The pregnancy was generally uncomplicated, and the subject delivered a healthy child with no abnormalitites on ----------. Delivery was by Caesarian section because of a previous C-section.

- **5-Day Solicited Local Reactions**
  - o Calculations were based on the Safety Population of 1357, 1089 total CSL IVV recipients and 268 Placebo recipients.
  - o The majority of subjects did not experience local reactions. The most common local reactions were tenderness, pain, erythema, and induration. CSL vaccine recipients experienced significantly more pain and tenderness than the placebo group. Only a few subjects reported severe reactions.

The following table is based on the applicant's Table 27 Module 5 Volume 1 Section 14, p226-255:

Table 8.1.1-24 Proportion and intensity of Solicited Local AEs within 5 days of vaccination CSLCT-FLU-05-09

Reaction	Both CSL IVV Presentations n = 1089 %	Placebo n = 268 %
Induration/ Swelling	9.2 ***(100 vs 101)***	0.7
Severe	0.1	0
Erythema/ Redness	16.3	8.2 ***(22 vs 23)***
Severe	0.2	0
Pain	39.8	9.3
Severe	0	0
Tenderness	59.8	17.9
Severe	0	0
Ecchymoses	4.8	1.1
Severe	0	0

% represents the proportion of subjects experiencing the reaction or severity in the respective group
Bold print=applicant's summary in paper submission
Bold italics=reviewer's results from electronic dataset evaluation

Reviewer comment: the applicant's numbers for subjects who experienced the events were nearly identical to those found by evaluating the electronic datasets. The reviewer found one more report of induration and one more report of erythema than the applicant (bold vs italic print). These findings did not affect the overall percentages of local reactions reported in the study, and will not affect the product labeling for safety. There were no obvious differences between the thimerosal-free and thimerosal-containing vaccine, and the table displays data from the four CSL vaccine groups compared to Placebo.

- **5-day Solicited Systemic Reactions**

  The most frequent solicited systemic reactogenicity events were headache, malaise, and myalgias. The majority of events were described as mild. Overall, the proportion of subjects experiencing solicited systemic AEs among the CSL vaccine and Placebo recipients was similar.

  The following table is based on the sponsor's Table 26 Module 5 Volume 1 Section 14, pp184-225:

Table 8.1.1-25 Frequency and intensity of Solicited Systemic AE's within 5 days of vaccine administration CSLCT-FLU-05-09

Reaction	Both CSL IVV Presentations n=1089 %	Placebo n=268 %
Fever	1.2	0.7
Severe	0	0
Headache	25.6 ***(279 vs 277)***	25.7
Severe	0.5	0.4
Malaise	19.5	18.7
Severe	0.5	0.4
Myalgias	12.9	9.0
Severe	0.2	0.7

Chills/ Shivering	3.0	2.2
Severe	0.1	0
Nausea	6.4	8.6
Severe	0.3	0.4

Vomiting	0.8	0.7
Severe	0.3	0.4

% = proportion of subjects with the AE
Bold print=applicant's summary in the paper submission
Bold italics=results of reviewer's evaluation of the electronic datasets

Reviewer comment: the reviewer found one discrepancy in the electronic datasets that yielded slightly different absolute numbers compared to the applicant's results (bold vs bold italics) of subjects experiencing headache, but these did not greatly influence the interpretation of systemic reactogenicity to be reported in the product labeling. No significant differences were found among the different lots and presentation of the CSL vaccine, and these are, therefore, grouped together in the above table.

• Summary of Solicited Local and Systemic Reactogenicity Events Occurring within 5 Days of Vaccination

The following table compares the severity of solicited reactogenicity events as reported by the applicant in the paper submission (Tables 26 and 27 Module 5 Vol 1, pp184-255) with the numbers found by reviewing the electronic datasets:

Table 8.1.1-26 Summary of Solicited Local and Systemic Adverse Events within 5 days of Vaccination, CSL vaccine versus Placebo and According to Severity, CSLCT-FLU-05-09

Solicited Adverse Event	All CSL n=1089 dataset		All CSL Applicant	Placebo N=268 dataset		Placebo Applicant
Local induration Swelling	n	n	E	n	n	E
Mild	90	90	91	2	2	2
Moderate	12	12	12	0	0	0
Severe	4	4	4	0	0	0
Total induration	106	100	***107***	2	2	2
Local erythema						
Mild	169	169	169	22	22	22
Moderate	13	13	13	0	0	0
Severe	2	2	2	0	0	0
Total erythema	184	178	184	22	22	22
Local vaccination Site pain						
Mild	418	418	422	25	25	26
Moderate	47	47	47	3	3	3
Severe	0	0	0	0	0	0
Total vaccination Site pain	465	433	***469***	28	25	29
Local tenderness						
Mild	640	640	647	48	48	51
Moderate	48	48	49	3	3	3

Severe	0	0	0	0	0	0
Total tenderness	688	651	***696***	51	48	***54***
Local ecchymosis						
Mild	44	44	45	3	3	3
Moderate	12	12	12	0	0	0
Severe	0	0	0	0	0	0
Total ecchymosis	56	52	***57***	3	3	3
Fever						
Mild	10	10	10	2	2	2
Moderate	3	3	3	0	0	0
Severe	0	0	0	0	0	0
Total fever	13	13	13	2	2	2
Headache						
Mild	250	250	278	59	59	68
Moderate	54	54	56	16	16	16
Severe	5	5	5	1	1	3
Total headache	309	279	***339***	76	69	80
Malaise						
Mild	196	196	211	45	45	49
Moderate	46	46	46	12	12	12
Severe	5	5	5	1	1	1
Total malaise	247	212	**262**	58	50	62
Myalgia						
Mild	125	125	136	21	21	24
Moderate	25	25	25	5	5	5
Severe	2	2	2	2	2	2
Total myalgia	152	140	***163***	28	24	31
Chills/shivering						
Mild	28	28	30	3	3	3
Moderate	6	6	6	3	3	3
Severe	1	1	1	0	0	0
Total chills	35	33	***37***	6	6	6
Nausea						
Mild	56	56	58	20	20	21
Moderate	16	16	16	5	5	5
Severe	3	3	3	1	1	1
Total nausea	75	70	***77***	26	23	27
Vomiting						
Mild	6	6	6	0	0	0
Moderate	2	2	2	1	1	1
Severe	3	3	3	1	1	1

Total vomiting	11	9	11	2	2	2

All CSL=all subjects receiving CSL IVV, either presentation
n=numbers of subjects in the respective group
E=number of events in the respective group as reported by the applicant in the paper submission
"Total" n for each solicited AE: If subjects had multiple events of the same intensity, it was counted only once. However, subjects could be counted more than once overall, for example, if they experienced the same reaction but with different degrees of severity post-vaccination.

Reviewer comment: For all solicited local and systemic AEs within 5 days of vaccination, the number of subjects experiencing reactions of a specific severity according to the datasets was exactly as reported by the applicant. "Total n" for the dataset columns represent the number of subjects experiencing a particular reaction with a specific severity. In some instances this number is greater than the "Total n" for the applicant column which counts each subject experiencing a reaction only once regardless of whether they experienced different degrees of severity. The total number of events for each category as reported by the applicant was higher than the number of subjects experiencing the event implying that some subjects had multiple episodes of the reaction over the 5 post-vaccination day period. This was especially true for headache, malaise, myalgias, and injection site pain and tenderness. The number of adverse events reported by the applicant for each category was higher than the number of events found in the electronic datasets. The reviewer, therefore, chose the number of events as reported by the applicant to display in the tables. This is a more conservative approach to safety and will be reported as such in the label.

- **Unsolicited Adverse Events**

The following table depicts all unsolicited events occurring in at least 1% of subjects in any treatment group, and is based on the applicant's Table 32, Module 5, Volume 1, Section 14, pp270-281, and modified by the Reviewer:

Table 8.1.1-27 Most frequent Unsolicited Events by Preferred Term Occurring in ≥1% of Subjects in at least one treatment group

Preferred Term	CSLmd Lot 1 n=273 %	CSLmd Lot 2 n=275 %	CSLmd Lot 3 n=275 %	CSLmd Lots 1/2/3 n=823 %	**Placebo n=268 %**	CSLpf Syringe n=266 %	**All CSL n=1089 %**
Headache	8.1	7.3	6.2	7.2	**5.6**	8.6	**7.5**
Dizziness	0.7	1.1	0.7	0.9	**0.4**	0.0	**0.6**
Sinus headache	1.1	0.4	0.0	0.5	**0.0**	0.4	**0.5**
Reactogenicity Event	3.3	4.4	2.2	3.3	**2.6**	3.0	**3.2**
Injection site bruising	0.4	0.0	1.8	0.7	**0.4**	0.0	**0.6**
Fatigue	1.1	0.4	0.4	0.6	**0.0**	0.0	**0.5**
URI	1.1	2.5	2.2	1.9	**0.7**	0.4	**1.6**
Nasopharyngitis	1.1	0.7	0.0	0.6	**0.0**	1.1	**0.7**
UTI	0.4	0.0	1.1	0.5	**0.0**	0.4	**0.5**

Back pain	2.2	1.1	1.5	1.6	**0.4**	1.9	**1.7**
Myalgia	0.7	1.5	2.2	1.5	**0.7**	1.1	**1.4**
Arthralgia	1.1	0.7	0.7	0.9	**0.7**	1.1	**0.9**
Pain in extremity	0.4	2.2	0.7	1.1	**0.4**	0.4	**0.9**
Muscle spasms	0.4	1.1	0.0	0.5	**1.1**	0.0	**0.4**
Diarrhea	3.7	2.5	0.7	2.3	**2.6**	1.1	**2.0**
Abdominal pain upper	0.7	0.4	1.5	0.9	**0.0**	0.4	**0.7**
Pharyngo-Laryngeal Pain	2.6	3.6	2.2	2.8	**1.1**	3.8	**3.0**
Nasal congestion	0.7	1.1	0.4	0.7	**1.1**	0.8	**0.7**
Rhinorrhea	0.4	0.4	1.5	0.7	**1.1**	0.8	**0.7**
Cough	1.1	0.4	0.7	0.7	**0.4**	0.8	**0.7**
Rash	1.5	0.4	0.7	0.9	**0.4**	1.1	**0.9**

Dermatitis contact	0.7	0.4	0.0	0.4	**0.7**	1.1	**0.6**

Dysmenorrhoea	1.8	0.4	1.1	1.1	**0.4**	0.4	**0.9**

n=number of subjects
% = percentage of subjects experiencing a particular AE
CSLmd Lot 1/2/3=CSL IVV thimerosal-containing multidose vial presentation, lots 1, 2, and 3
CSL pf syringe=CSL IVV pre-filled syringe thimerosal-free presentation
URI=upper respiratory tract infection
UTI=urinary tract infection

Reviewer comment: Headache was the most common unsolicited AE among CSL IVV recipients followed by reactogenicity events, pharyngolarygeal pain, diarrhea, back pain, upper respiratory infection, and myalgia. Overall, the frequency of these events was similar among the four CSL IVV groups and between CSL IVV and Placebo. The applicant also reported that most of these events were mild or moderate in severity. Review of the electronic datasets confirmed that the number of subjects experiencing the specific AEs were identical to the applicant's report.

- **Unsolicited AEs according to Severity and Relationship to Study Vaccine**

The following table was modified modified from applicant's Table 29 Module 5 Volume 1 Section 14, p266. N refers to the number of subjects rather than the number of events:

Table 8.1.1-28 Summary of Unsolicited Adverse Events According to Severity and Relationship to Vaccine Reported by the Applicant CSLCT-FLU-05-09

	All CSL Vaccine n=1089			Placebo n=268	
	%	E		%	E
Subjects (%)	33.4	552		28.0	132
Unsolicited AEs		552			132
Severity					
Mild	23.2	350		17.9	76
Mod	14.0	191		12.7	49
Severe	0.9	11		1.9	7
Life threatening	0	0		0	0
Death	0	0		0	0
Vaccine-Related					
Yes	10.3	146		8.2	36
No	26.1	406		22.4	96

% based on number of subjects
E=number of events of a given severity in the respective group

Unsolicited AEs were predominantly mild or moderate, 23.2% and 14.0% for CSL IVV recipients and 17.9% and 12.7% for the placebo group respectively. 0.9% of CSL IVV subjects and 1.9% of placebo subjects experienced severe AEs. Association with the vaccine was somewhat greater in the CSL vaccine group than placebo, 10.3% vs 8.2%. There were no life-threatening AEs or deaths. There were no obvious differences when evaluating safety among thimerosal-containing lots and thimerosal-free pre-filled syringe.

The Medical Officer's evaluation of the electronic datasets confirmed the above and is presented in the table below:

Table 8.1.1-29 Summary of Unsolicited AEs according to Severity and Relationship to Vaccine based on the Datasets

	CSL IVV* (reviewer)		CSL IVV* (applicant)		Placebo (reviewer)		Placebo (applicant)	
	N	E	N	E	N	E	N	E
No. unsolicited AEs	364	552	364	552	75	132	75	132
AE severity								
Mild	253	350	253	350	48	76	48	76
Moderate	152	191	152	191	34	49	34	49
Severe	10	11	10	11	5	7	5	7
Life threatening	0		0		0		0	
Death	0		0		0		0	
AE relationship to Vaccine								
Associated	112	146	112	146	22	36	22	36
Not associated	284	406	284	406	60	96	60	96

*CSL IVV=all four groups, thimerosal and thimerosal-free, have been combined
Reviewer=data derived from evaluation of datasets
Applicant=data derived from applicant's summary in paper submission

Reviewer comment: there was one serious AE recorded in the datasets, subject 27FCI154, female who was assaulted and suffered a fractured femur. This case was reviewed in Section 8.1.1.2.3.

- **Unsolicited Adverse Events by System Organ Class**

The Medical Officer reviewed Unsolicited AEs during the 21 days post-vaccination. There were 684 line listings among 439 subjects. The following table is based on Table 31 Module 5 Volume 1 Section 14, p 268 and was confirmed by review of the electronic datasets:

Table 8.1.1-30 Unsolicited AEs Occuring within 21 days of Vaccination, by System Organ Class

SOC	All CSL IVV n, reviewer (applicant)	Placebo n, reviewer (applicant)	Total
#AEs	552 (552)	132 (132)	684
Nervous System	115 (115)	25 (25)	140
General/ Admin site	75 (75)	18 (18)	93
GI	59 (59)	20 (20)	79
MS/ConnTiss	67 (67)	12 (12)	79
Respiratory, thoracic, and mediastinal ds	65 (65)	13 (13)	78
Infections and infestations	59 (59)	16 (16)	75
Skin and subcutaneous Tissue disorders	33 (33)	6 (6)	39
Injury, poisoning, and Procedural complications	29 (29)	4 (4)	33
Reproductive system and breast	17 (17)	5 (5)	22
Psychiatric disorders	12 (12)	3 (3)	15
Immune system disorders	3 (3)	3 (3)	6
Ear and labyrinth disorders	3 (3)	2 (2)	5
Surgical and medical procedures	2 (2)	3 (3)	5
Eye disorders	2 (2)	2 (2)	4
Investigations	3 (3)	0 (0)	3
Blood and lymphatic System disorders	2 (2)	0 (0)	2
Metabolism and nutrition Disorders	2 (2)	0 (0)	2
Renal and urinary disorders	2 (2)	0 (0)	2

Social circumstances	1 (1)	0 (0)	1
Vascular disorders	1 (1)	0 (0)	1
Total	552 (552)	132 (132)	684

• **Most Frequently Reported Adverse Events by SOC and Preferred Term**

The following tables are based on the applicant's Table 32 Module 5 Volume 1 Section 3.5.1-1, p270, and results confirmed by review of the electronic datasets:

Table 8.1.1-31 Nervous System Disorders

AE	All CSL N=1089 n (%)	E	Placebo N=268 n (%)	E	Total events
All	97 (8.9%)	114 ***115***	19 (7.1%)	25	139 ***140***
Headache	82 (7.5%)	95 ***96***	15 (5.6%)	21	116
dizziness	7 (0.6%)	7	1 (0.4%)	1	8
Sinus h/a	5 (0.5%)	6	0 (0%)	0	6
Other*	6 (0.6%)	6	3 (1.1%)	3	9

n=number of subjects
E=number of events
% based on the number of subjects in each group

Reviewer comment: there appeared to be a greater proportion of headaches in both the CSL vaccine and placebo groups, somewhat more in the CSL vaccine group.
The values reported by the applicant were confirmed by evaluation of the electronic datasets. Instances where the applicant's data differs from the reviewer are indicated in bold italics. Overall, the number of subjects and events reported by the applicant are consistent with the datasets.

*Three of the "Other" subjects in the CSL group experienced two different preferred term AE's and are only counted once (as 3 instead of 6 so that "All" subjects experiencing an AE = 97, not 100.)

Table 8.1.1-32 General disorders and administration site conditions

Adverse event	All CSL n=1089 n (%)	E	Placebo n=268 n (%)	E	Total events
all	69 (6.3)	75	16 (6.0)	18	93
Reactogenicity event	35 (3.2)	36	7 (2.6)	7	43
Pain	8 (0.7)	8	2 (0.7)	2	10
Injection site bruising	6 (0.6)	6	1 (0.4)	1	7

Fatigue	5 (0.5)	5	0 (0)	0	5
Injection site pain	0 (0%)	0	1 (0.4%)	1	1
Other*	19 (1.7)	20	6 (2.2%)	7	27

n=number of subjects
E=number of events
% based on number of subjects in each group

Reviewer comment: "pain" is distinguished from injection site pain. The occurrence of general and administration site events was similar between the two groups. These data were confirmed by review of the electronic datasets.
*Subject 27FIW103 experience 4 different preferred term AEs, subject 27DST160 experienced 2 different AEs. They are counted only once as part of the total number of subjects experiencing an AE ("All"), so that this number is 69 rather than 73.

Table 8.1.1-33 Infections and infestations

Preferred term	All CSL n=1089 n (%)	E	Placebo N=268 n (%)	E	Total events
All	56 (5.1%)	59	16 (6.0%)	16	75
Upper respiratory Infection	17 (1.6%)	18	2 (0.7%)	2	20
Nasopharyngitis	8 (0.7%)	8	0 (0)	0	8
Viral infection	4 (0.4%)	4	4 (1.5%)	4	8
Cellutitis	1 (0.1%)	1	0 (0)	0	1
Other*	28 (2.6%)	28	10 (3.7%)	10	38

n=number of subjects
E=number of events
% based on number of subjects in each group

Reviewer comment: The overall frequency was low in both groups. There were slightly more URIs in the CSL group than placebo and slightly more viral infections among the placebo recipients. There was only one case of cellulitis which occurred in subject #27FVD167. This was due to an excoriation, judged non-vaccine-related, and was ongoing at visit 3. These results were confirmed by review of the ------ database.
*Two subjects experienced 2 different AEs by preferred term, but are counted only once as part of the total or "All" subjects who experienced an AE. This number is therefore 56 rather than 58.

Table 8.1.1-34 Musculoskeletal and connective tissue disorders

Adverse event	All CSL N=1089 n (%)	E	Placebo N=268 n (%)	E	Total events
All	62 (5.7%)	67	9 (3.4%)	12	79
Back pain	18 (1.7%)	19	1 (0.4%)	1	20
Myalgia	15 (1.4%)	15	2 (0.7%)	2	17
Arthralgia	10 (0.9%)	10	2 (0.7%)	2	12

Pain in extremity	10 (0.9%)	10	1 (0.4%)	1	11
Muscle spasms	4 (0.4%)	5	3 (1.1%)	5	10
Other *	8 (0.7%)	8	1 (0.4%)	1	9

n=number of subjects
E=number of events
% based on number of subjects in each group

Reviewer comment: There were slightly more episodes of back pain and myalgias in the CSL IVV group and more muscle spasms in the Placebo group, but the overall frequency of these events was low. Review of the ------ database confirmed the applicant's numbers.

*For the Placebo group, the total number of subjects experiencing a musculoskeletal or connective tissue disorder was nine. However, subject 27FSL246 had both neck pain ("other") and pain in an extremity. Thus, in ------, there are 9 subjects in the placebo group with 10 different preferred term AE's. If one counts the subject with 2 different preferred term AEs only once as does the applicant, then the dataset values for "All" are identical to the applicant's.

Table 8.1.1-35 Gastrointestinal disorders

Adverse event	All CSL N=1089 n (%)	E	Placebo N=268 n (%)	E	Total Events
All	53 (4.9%)	59	14 (5.2%)	20	79
Diarrhea	22 (2.0%)	22	7 (2.6%)	9	31
Abdominal pain upper	8 (0.7%)	8	0 (0%)	0	8
Nausea	4 (0.4%)	4	2 (0.7%)	2	6
Other *	24 (1.8%)	25	9 (0.7%)	9	34

n=number of subjects
E=number of events
% based on number of subjects in each group

The applicant's numbers were confirmed by review of the electronic datasets.
*Four of the "other" AEs in the placebo group were experienced by subjects who also had diarrhea. These 4 subjects are only counted once under number of subjects with any AE. (This again is why the n's don't add up to the "All" in the placebo group. One must subtract 4 from 18.) Similarly, 5 of the "other" subjects in the CSL group experienced more than one preferred term AE and therefore only 24 – 5 = 19 subjects are counted as "other" in order to derive the total of 53 subjects in the CSL group experiencing an AE.

Table 8.1.1-36 Respiratory and Thoracic

Adverse event	All CSL N=1089 n (%)	E	Placebo N=268 n (%)	E	Total events
All	55 (5.1%)	65	11 (4.4%)	13	78
Pharygolaryngeal pain	33 (3.0%)	34	3 (1.1%)	3	37
Nasal congestion	8 (0.7%)	8	3 (1.1%)	4	12

Rhinorrhea	8 (0.7%)	8	3 (0.1%)	3	11
Cough	8 (0.7%)	8	1 (0.4%)	1	9
Other *	7 (0.6%)	7	2 (0.7%)	2	9

n=number of subjects
E=number of events
% based on number of subjects in each group

Reviewer comment: AEs in this group were generally similar with somewhat proportionately more overall events and pharyngolaryngeal pain in the CSL IVV group.
*Nine subjects in the CSL group and 2 subjects in the placebo group had more than one type of AE by preferred term, but were counted only once as subjects having any AE. Therefore, total number of subjects experiencing any AE is 55 rather than 64.

Table 8.1.1-37 Skin and subcutaneous tissue disorders

Adverse event	All CSL N=1089 n (%)	E	Placebo N=268 n (%)	E	Total
All	30 (2.8%)	33	5 (1.9%)	6	39
Rash	10 (0.9%)	11	1 (0.4%)	1	12
Dermatitis contact	6 (0.6%)	6	2 (0.7%)	2	8
Pruritis	4 (0.4%)	4	1 (0.4%)	1	5
Urticaria	1 (0.1%)	2	0 (0)	0	1
Rash macular	1 (0.1%)	1	0 (0)	0	1
Rash pruritic	0 (0)	0	1 (0.4%)	1	1
Other *	9 (0.9%)	9	1 (0.4%)	1	11

n=number of subjects
E=number of events
% based on number of subjects in each group

Reviewer comment: Adverse skin and subcutaneous reactions between the CSL IVV and Placebo groups were similar. Of 39 events, 33 occurred in the CSL IVV recipients. Of these, 11 events in 9 CSL recipients were felt to be vaccine associated. Most of these were mild rashes and/or pruritis. No additional cases of cellulitis were found. Review of ------ database confirmed the number of subjects and events reported in the paper submission.

*One subject in the CSL group experienced two different types of AE's by preferred term contributing to an "Other" of 9, but was only counted as one subject in the "All" CSL subjects having an AE. The total CSL recipients with any AE in this SOC is therefore 30 instead of 31. One subject in the placebo group had 2 different AEs by preferred term, but was counted only once in "All" subjects experiencing any AE.

Table 8.1.1-38 Immune system disorders

Adverse event	All CSL N=1089 n (%) E	Placebo N=268 n (%) E	Total events	Severity	Vaccine Association

All	3 (0.3%) 3	2 (0.7%) 3	6		
Multiple allergies	1 (0.1%) 1	1 (0.4%) 2	3	Mild	No
Hypersensitivity	0 (0) 0	1 (0.4%) 1	1	Mild	No
Seasonal allergies	1 (0.1%) 1	0 (0) 0	1	Mod	No
Serum sickness	1 (0.1%) 1	0 (0) 0	1	Mod	Yes

n=number of subjects
E=number of events
% based on number of subjects in each group

Reviewer comment: The frequency of immune disorders was very low in both CSL IVV and placebo recipients, and they were mostly mild to moderate in severity. Only one event was felt to be vaccine associated, the case of serum sickness in subject 27FVD137 discussed under AEs of special interest in Section 8.1.1.2.3 above. See review of line listings below. Results presented in the paper submission were confirmed by review of the JMP database.

- **Review of Severe Unsolicited Adverse Events and Relationship to Study Vaccine**

Only one vaccine-associated severe unsolicited AE was reported by the applicant. This consisted of treatment-emergent diarrhea which resolved without sequelae occurring in subject 27 FCI151 who received Placebo vaccine.

The remaining 15 severe unsolicited AEs were reported as being non-vaccine-associated by the applicant. Eleven events occurred in ten of the CSL vaccine recipients, and seven events occurred in five placebo recipients. Among the CSL recipients, these included enteroviral infection (n=1), viral gastroenteritis (n=1), viral infection (n=1), arthropod sting (n=1), excoriation (n=1), femur fracture (n=1), muscle spasms (n=1), myalgias (n=1), headache (n=1), migraine (n=1), and nephrolithiasis (n=1).

The following table is based on the applicant's text p 75 and Table 33 p 282, both Module 5 Volume 1, and listings 9.1, 9.1.1, and 9.2 (Adverse events, alternative etiology of non-associated events, and associated AEs). The CRF for the single SAE, subject 27FCI154, was also reviewed:

Table 8.1.1-39 Applicant's report of Severe Adverse Events

Subject	Treatment	Severe AE	Vaccine association	Outcome
27FCI154	CSLmd Lot 1	Skin abrasions following assault	No	Resolved
27FVD031	CSLmd Lot 1	Viral infection	No	Resolved
27FVD035	CSLmd Lot 1	Viral gastroenteritis	No	Resolved
27FVD090	CSLmd Lot1	Enteroviral	No	Resolved

		infection		
FBA007	CSLmd Lot 2	Muscle spasm, thigh	No	Resolved
FDU035	CSLmd Lot 2	Migraine headache	No	Resolved
27FBA031	CSLpf syringe	Wasp sting	No	Resolved
27FBA059*	CSLpf syringe	Headache	No	Resolved
27FBA020	Placebo	R patellar injury	No	Ongoing
27FCI151	**Placebo**	**Intermittent diarrhea**	**Yes**	**Resolved**
FSL246	Placebo	Pain L leg	No	Resolved
27FST111	Placebo	Migraine headache	No	Resolved

*Reviewer comment: Subject 27FBA059 could not be located in listing 5 for the Visit 01 vaccination date, nor in the listing 9.1.1 for an alternate etiology of the AE. The explanation for this appeared to be an error in the prose/text on p70. The subject ID was actually 27FBA056.

Reviewer comment: the following table was compiled by the Medical Officer from review of the electronic datasets and confirms the applicant's report:

Table 8.1.1-40 Unsolicited Severe Adverse Events Derived from the Medical Officer's Review of the Electronic Datasets

Subject	Tx	Severe AE	System organ class	Vaccine Association	Outcome
27FCI154	CSLmd Lot 1	R femur fracture	Injury, poisoning and procedural complications	No	Ongoing
27FCI154	CSLmd Lot 1	Excoriations	Injury, poisoning and procedural Complications	No	Not specified
27FVD031	CSLmd Lot 1	Viral infection	Infections and Infestations	No	Resolved
27FVD035	CSLmd Lot 1	Viral gastroenteritis	Infections and Infestations	No	Resolved
27FVD090	CSLmd Lot 1	Enteroviral gastroenteritis	Infections and Infestations	No	Resolved
27FBA007	CSLmd Lot 2	R thigh muscle spasm	Musculoskeletal and CT disorders	No	Resolved
27FDU035	CSLmd Lot 2	Migraine headache	Nervous system Disorders	No	Resolved
27FUM092	CSLmd Lot 3	Sore muscle R shoulder	Musculoskeletal and CT	No	Resolved

			disorders		
27FBA020	Placebo	L patellar injury	Musculoskeletal and CT disorders	No	Ongoing
27FCI050	Placebo	Pain related to oral cyst removal	Surgical and medical procedures	No	Ongoing
27FCI151	**Placebo**	**Diarrhea**	**GI disorders**	**Yes**	**Resolved**
27FCI151	Placebo	Intermittent diarrhea	GI disorders	No	Resolved
27FCI151	Placebo	Thrush mouth	Infections and infestations	No	Resolved
27FSL246	Placebo	L leg pain with mild sensory loss	Musculoskeletal and CT disorders	No	Resolved
27FST111	Placebo	Migraine with aura	Nervous system disorders	No	Resolved

27FBA031	CSLpf syringe	Wasp sting	Injury, poisoning and procedural complications	No	Resolved

27FBA056	CSLpf syringe	Headache	Nervous system disorder	No	Resolved
27FCI101	CSLpf syringe	Kidney stone	Renal and urinary disorders	No	Resolved

Tx = treatment

Subject 27FCI151 with diarrhea initially attributed to the vaccine, but subsequently given alternative diagnosis of gastroenteritis. This subject received placebo. No additional comments in database.

Subject 27FSL246 was felt to have a possible neuropathy. This subject received placebo and symptoms were attributed to an L4 radiculopathy and DJD.

Subject 27FBA056 with severe headache had received CSL IVV pre-filled syringe. Symptoms were attributed to a migraine headache triggered by menses.

Subject 27FDU035 received CSL multidose Lot 2 on July 5, 2006 and had onset of severe migraine headache on July 6, 2006. According to the applicant, the subject had history of migraine headaches, and the headache was already present at vaccination.

- **Case Report Forms Reviewed for Study CSLCT-FLU-05-09**

  - Subject 27FCI154, a 42 year old female, received CSL IVV multidose vial Lot 1 on July 11, 2006. On ----------, the subject was the victim on an assault, suffered a fracture of the right femur, and was hospitalized. She received a tetanus shot on ----------, and underwent internal fixation of the femur. She was discharged on ---------- and subsequently fully recovered. This SAE was judged not associated with the study vaccine.

  - Subject 27FVD137 Serum sickness - a 32 year old male was vaccinated with CSL thimerosal-containing multidose vial vaccine Lot 3 on July 14, 2006. He had received influenza vaccine for the previous four years. On Day 1 post-vaccination, the subject developed erythematous papules on exposed areas of skin which over the ensuing weeks evolved into an allergic type reaction consisting of hives, urticaria, dermatographism and arthralgias, "moderate" in severity. He was treated with oral anti-histamines, was referred to an allergist, and on September 15, 2006, was begun on oral prednisone. Symptoms recurred with steroid taper, but responded to a second course of steroids. Follow up in January and April 2007 revealed persistent dermatographism and skin reactivity to placebo which precluded allergy skin testing with Flumist. The subject also continued to experience occasional urticaria which were treated with oral anti-histamines as needed. The outcome of this event was recorded as "resolved with sequelae" and the event was considered to be "associated" with the study vaccine.

  Reviewer comment: it is difficult to know whether this is truly a case of serum

sickness. The CRF describes the rash as excoriated papules and urticaria. Onset 1 day after vaccination and ongoing urticaria from July 15, 2006 to April 2007 would be unusual. Results of laboratory investigation, biopsies, or specialist consultation are not provided. Two other cases of serum sickness are reported in the post-marketing experience and serum sickness will be included in the label.

o Subject 27FVD153 Pregnancy - a 27 year old female was vaccinated with CSL thimerosal-containing multidose vial vaccine Lot 3 on July 26, 2006. Urine pregnancy test on the day of vaccination was negative, but both urine and serum pregnancy tests were positive on Visit 3 Day 21, August 16, 2006. The pregnancy was generally uncomplicated, and the subject delivered a healthy child with no abnormalitites on ----------. Delivery was by Caesarian section because of previous C-section.

• **Vital Signs and Physical Exam**

Subject 27FSL051 had a BP of 84/58 and was to receive CSL pre-filled syringe. Subject stated that this BP was normal for her. She was vaccinated without immediate adverse reactions.

• **Laboratory evaluation**

No clinical laboratories were performed for this study except for screening and/or visit 1 pregnancy tests which were to be negative within 24 hours of vaccination. One subject, 27FVD153, became pregnant after vaccination. The CRF was reviewed in the above section Review of CRFs.

Comments and Conclusions of Study CSL-CT-FLU-05-09

o Study CSL-CT-FLU-05-09/DMID 06-0016 was the pivotal Phase III, randomized, double-blind, placebo-controlled, multi-center study to evaluate the immunogenicity, safety, and tolerability of CSL IVV in adults aged ≥ 18 to < 65 years. The data from the study appear to have integrity and to support licensure.

o The study met the pre-defined success criteria for the co-primary endpoints. The lower bound of the 95% CI for the proportion with HI antibody titer exceeded 70% for each strain: 96.7%LB for A/H1N1; 99.5%LB for A/H3N2; and 92.7%LB for B strain. The lower bound of the 95% CI for the seroconversion rate exceeded 40% for each strain: 45.6% for A/H1N1; 68.7% for A/H3N1; and 66.9% for B strain.

o Regarding secondary endpoints, logistic regression analysis of the co-primary endpoint data was used to derive geometric mean titers and GMT ratios in order to demonstrate lot-to lot consistency between the multidose and the pre-filled syringe presentations and as further evidence that the data were robust.

o Regarding the safety evaluation, a potential limitation of the study was the 21-day follow-up which may have failed to capture long-term serious neurologic sequelae or new chronic

medical conditions. To be able to conduct a review of a BLA that is submitted in a reasonable time frame in order for licensure for the 2007-2008 influenza vaccine season, longer term safety follow up in this study would not have been feasible. Study close-out would have occurred first or second quarter 2007 and would not have permitted BLA submission in April 2007. Furthermore, the vaccine was licensed in over 20 countries worldwide, and post-marketing safety experiences on serious adverse events was available.

o Regarding safety results, there were no deaths or vaccine-associated SAEs during the study. The single SAE which occurred in a CSL vaccine recipient was the result of an assault and was not attributed to the vaccine. No severe AEs were associated with CSL IVV. One case of possible serum sickness, moderate in severity, was attributed to the vaccine. One subject became pregnant during the study and delivered a healthy baby. No subject withdrew from the study because of a vaccine-associated adverse event.

o Of the 552 unsolicited AEs occurring in CSL vaccine recipients, the majority were mild (23.2% of all CSL IVV recipients) or moderate (14.0% of all CSL IVV recipients). Headache, pharyngolarygeal pain, diarrhea, back pain, upper respiratory infection, and myalgia occurred with a frequency of ≥1% in CSL recipients. Of reactogenicity events, myalgias, pharyngolaryngeal pain and rash occurred slightly more often in CSL IVV recipients than in the placebo group. Only 10 subjects or 0.9% of CSL recipients experienced 11 severe AEs. Of these, none were vaccine-related.

o Of local and systemic reactogenicity events, headache, malaise, myalgias, and nausea occurred with a frequency of ≥ 5% in both CSL vaccine and placebo groups. Myalgias were slightly more frequent in the CSL group relative to placebo. These events were mostly mild to moderate in severity, and the majority of subjects did not experience any adverse reactogenicity events.

o Overall, the safety and efficacy data appear to have integrity and support licensure. Vaccination with both the multidose and pre-filled syringe presentations of CSL IVV produced an immune response which exceeded the co-primary endpoint criteria and which demonstrated lot-to-lot consistency. No unexpected safety signals or unusual patterns of adverse events were noted. This study would support accelerated approval for licensure of Afluria for prevention of influenza disease.

o Post-marketing clinical endpoint culture-confirmed efficacy studies in young healthy adults and immune response and safety studies in special populations such as children, adults at risk for complications of influenza, and in the elderly should be undertaken to support traditional approval. Because the Hispanic/Latino population appears to have been underrepresented in this study, the applicant should be encouraged to enhance the numbers of these subjects in its post-marketing studies. The duration of safety follow-up in these studies should be six months.

8.1.2 Trial # 2

8.1.2.1 Applicant's Protocol Number CSLCT-NHF-05-15

"A Phase IV, randomized, observer-blind, comparator-controlled, single centre study to evaluate the immunogenicity, safety, and tolerability of CSL influenza vaccine (Enzira®) (2006/2007) in Healthy Older Adults Aged ≥ 65 Years."

8.1.2.1.1 Objective/Rationale

• The Primary Objective was to demonstrate that vaccination with CSL influenza vaccine (CSL IVV), heretofore identified as Enzira 2006/2007, produced an immune response sufficient to meet the CPMP criteria for older adults of:
  - the proportion with a post-vaccination four-fold increase in anti-HI antibody titer of at least 1:40, 21 days following vaccination, of > 30%, and
  - the proportion with a post-vaccination anti-HI antibody titer ≥ 1:40 of >60%.

• Secondary objectives included:
  - To demonstrate that CSL IVV 2006/2007 was no more reactogenic than GlaxoSmithKline Influenza Vaccine (heretofore identified as Fluarix or Influsplit) 2006/2007 in healthy older adults aged ≥ 65 years.
  - To demonstrate that vaccination with CSL IVV 2006/2007 produced an immune response in healthy older adults aged ≥ 65 years sufficient to meet the criteria of the *CPMP/BWP/214/96 Note for Guidance on Harmonisation of Requirements for Influenza Vaccines* in older adults.

8.1.2.1.2 Design Overview:

• The study was a Phase IV, randomized, observer-blind, comparator-controlled, single-center study which planned to enroll up to 400 healthy older adults ≥ 65 years of age. Subjects were randomized 3:1 to receive Enzira or Influsplit at Chiltern a single research site in Slough, United Kingdom, for a study period beginning October 27, 2006 and ending December 29, 2006. Each participant had two scheduled visits, Day 0 for pre-vaccination anti-HI antibody titers followed by vaccination, and Day 21 (+ 4 days) for exit evaluation and post-vaccination anti-HI antibody titers. The maximum active study duration for each participant was 21 + 4 days. Subjects were observed for 30 minutes post-vaccination and were then issued a 5-day diary card for Solicited Adverse Events (AEs) and a 21-day diary card for Unsolicited AEs. Participants experiencing signs/symptoms of an intercurrent flu-like illness (ILI) between Days 0 and 21 were asked to return for an additional medical evaluation and nasal specimens for viral isolation. The study was approved by ----------

• The annual clinical trial required for registration in Europe is set forth in the CPMP/BWP/214/96 guideline, and is a non-comparator trial evaluating the safety and immunogenicity of the updated Northern Hemisphere trivalent vaccine formulation as determined by the World Health Organization (WHO) in healthy adult and elderly populations. CSL conducted an Annual Variation study to meet this requirement in the 2006/2007 season under protocol CSLST-NHF-05-13 with

Enzira. The results of this study showed an unusually high number of older adults without a boost in HI antibody titer against the H1N1 A/New Caledonia/20/99 virus strain relative to other vaccines licensed in the EU. A subset analysis suggested that the lower than expected seroconversion rate and overall immunogenicity outcome might be due to the impact of pre-existing serum antibody and/or previous influenza vaccination history. Subset analysis of older subjects without evidence of significant pre-existing immunity exceeded the CPMP criterion for geometric fold increase for the H1N1 strain, 2.19, but the sample size of 43 older adult participants was smaller than the CPMP guideline of 50 subjects. Protocol CSLCT-NHF-05-15 was therefore designed to assess the impact of pre-existing antibody titers and prior vaccination history on the serum antibody response to vaccination with influenza virus vaccine in older adults ≥ 65 years and for the H1N1 A/New Caledonia/20/99 strain in particular. To this end, the sample size for this study was expanded beyond the CPMP requirement of 50 participants and a comparator control was included.

8.1.2.1.3 Population

- The study planned for 400 subjects ≥ 65 years of age at a single study site in Slough, UK.
- **Inclusion criteria:**
  - Healthy males or females, aged ≥ 65 years at the time of providing informed consent;
  - Provision of written informed consent to participate in the study and willingness to adhere to all protocol requirements;
  - Good health as determined by medical history and physical examination where indicated;
  - Ability to understand and comply with planned study procedures.
- **Exclusion criteria:**
  - Hypersensivitviy to eggs, chicken protein, neomycin, polymyxin, gentamicin sulphate, formaldehyde, sodium deoxycholate, thiomersal or any components of the study vaccines;
  - Interpandemic vaccination against influenza or laboratory culture confirmed influenza in 2006;
  - Vaccination with an experimental influenza vaccine (eg. a candidate pandemic influenza vaccine or a novel influenza vaccine) in 2006.
  - Acute clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality.
  - Known history of Guillain-Barré Syndrome.
  - Clinical signs of active infection and/or an oral temperature of ≥ 38°C (100.4°F). Study entry could have been deferred for such individuals, at the discretion of the Principal Investigator (PI).
  - Active neurological disease.
  - Confirmed or suspected immunosuppressive condition (including cancer), or a previously diagnosed (congenital or acquired) immunodeficiency disorder.
  - Current treatment with warfarin or other anticoagulant.
  - Current (or within the 90 days prior to receiving the Study Vaccines) immunosuppressive or immunomodulative therapy, including systemic

corticosteroids, as follows:

• Chronic or long term corticosteroids: > 15 mg/day of oral prednisolone or equivalent daily.

• Sporadic corticosteroids: > 40 mg/day of oral prednisolone or equivalent for more than two courses of > 14 days in the three months preceding vaccination.

• Administration of immunogobulins and/or any blood products within the 3 months preceding the administration of the Study Vaccine or during the study.

Note: Use of topical or inhalant corticosteroids prior to administration of the Study Vaccines or throughout the Study was acceptable.

o Participation in a clinical trial where the participant received an investigational product or use of an investigational compound (i.e. a new chemical or biological entity not registered for clinical use) within 30 days prior to receiving the Study Vaccines or planed to enter a clinical trial during the study period.

o Vaccination with a registered vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to receiving the Study Vaccines.

o Current treatment or treatment with cytotoxic drugs or radiotherapy at any time during the six months prior to administration of the Study Vaccines.

o Major congenital defects or serious chronic illness.

o Evidence, or history (within the previous 12 months) of drug or alcohol abuse.

o Unwillingness or inability to comply with the study Protocol.

o History of psychiatric disorders, which, in the opinion of the PI, would prevent participants from giving proper informed consent.

8.1.2.1.4 Products mandated by the protocol:

• A single 0.5mL dose of trivalent influenza vaccine was administered by intramuscular or deep subcutaneous injection into the deltoid region of the upper arm contralateral to where the blood sample was collected when possible.

• **Table 8.1.2-1 Influenza vaccines used in trial CSLCT-NHF-05-15**

Group	Vaccine	Formulation	Lot number
A	Enzira	0.5 pre-filled syringe	CTSLNHF0515
B	Influsplit (GSK)	0.5 pre-filled syringe	AFLUA188AB AFLUA188AA

• Both vaccines consisted of split virion, inactivated influenza virus, propagated in hen's eggs, and contained the following three antigen strains recommended for the 2006/2007 Northern Hemisphere season:

o 15µg A/New Caledonia/20/99 (H1N1-like) virus (A/New Caledonia/20/99 IVR-

116);

o 15 µg A/Wisconsin/67/2005 (H3N2)-like virus (A/Hiroshima/52/2005 IVR-142;

o 15 µg B/Malaysia/2506/2004-like virus (B/Malaysia/2506/2004).

A total of 45 µg of hemagglutinin influenza antigen.

8.1.2.1.5 Endpoints

Table 8.1.2-2 Study Procedures and Assessments

60 (100%)
59 (98.3%)

• On Visit 1, Study Day 0, subjects underwent a medical evaluation including general medical history, history of previous influenza illness and vaccination, physical exam if clinically indicated, oral body temperature determination, and phlebotomy for anti-HI antibody titers prior to vaccination with Study vaccine. Subjects were monitored for adverse reactions for 30 minutes post-vaccination.
• Subjects were issued a 5-day Solicited AE diary card (for Days 0-4) to record oral temperature, local and systemic reactogenicity and a 21-day Unsolicited AE diary card for Days 0-20. These were to be mailed back to the investigator on Day 8 for review. Signs and symptoms of flu-like illness during the 21 day study period were to be reported immediately with subsequent medical evaluation and attempts at viral isolation within three days at the investigational site. The Exit Evaluation Visit on Day 21 + 4 consisted of collection of the post-vaccination anti-HI antibody titers, a review of AEs/SAEs by a blinded investigator/delegate, and a brief medical evaluation including concomitant medications and physical exam if indicated.
• All AEs and SAEs were recorded in the CRFs.
• Solicited Local and Systemic reactogenicity were graded according to the following scales:

Table 8.1.2-3 Solicited AE Grading Scale

LOCAL SYMPTOMS	INTENSITY GRADING (Diameter)			
	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	
Pain	Does not interfere with activity	Interferes with activity	Prevents daily activity	
Tenderness	Does not interfere with activity	Interferes with activity	Prevents daily activity	

LOCAL SYMPTOMS	INTENSITY GRADING (Diameter)			
	0	1	2	3
Erythema (Redness)	0	< 20mm	≥ 20mm - ≤ 50mm	> 50mm
Induration (Hard Lump)	0	< 20mm	≥ 20mm - ≤ 50mm	> 50mm
Swelling	0	< 20mm	≥ 20mm - ≤ 50mm	> 50mm
Ecchymosis (Bruising)	0	< 20mm	≥ 20mm - ≤ 50mm	> 50mm

GENERAL SYMPTOMS	INTENSITY GRADING (Diameter)				
	No Symptom (Grade 0)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	
Fever	<37.7 °C	≥37.7 - <38.0 °C		≥38.0 - <39.0 °C	≥39.0°C
Headache	None	Does not interfere with activity		Interferes with activity	Prevents daily activity
Malaise	None	Does not interfere with activity		Interferes with activity	Prevents daily activity
Myalgia	None	Does not interfere with activity		Interferes with activity	Prevents daily activity
Chills	None	Does not interfere with activity		Interferes with activity	Prevents daily activity
Nausea	None	Does not interfere with activity		Interferes with activity	Prevents daily activity
Vomiting	None	Does not interfere with activity		Interferes with activity	Prevents daily activity

• Serious Adverse Events (SAEs) were 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
Was a medically significant event, judged by the treating physician to potentially jeopardize the participant or require medication intervention to prevent one of the outcomes defined as an SAE.

Surveillance Monitoring

• All AEs were reported to the Chiltern Study Monitor
• All SAEs including deaths were reported to the Chiltern Pharmacovigilance Officer within 24 hours. Unexpected SAEs and deaths were reported to the Independent Ethics Committee.
• Relationship of an AE to the study vaccine was categorized as not related, unlikely, possibly, probably, or definitely.
• Follow-up of AEs and SAEs was to be until resolution or stabilized.

8.1.2.1.6 Statistical considerations

• Analyses of the safety data were performed on the Safety Population defined as all participants who received a Study Vaccine on Day 0.
• Analyses of the immunogenicity data were performed on the Evaluable Population defined as all participants who were vaccinated on Day 0, provided both pre- and post-vaccination blood samples, and were not excluded from analyses due to use of a prohibited medication. Participants with laboratory confirmed flu-like illness at any time were also excluded from the Evaluable Population.
• Per Protocol Population (PP): in the event that a large number of protocol violations/deviations occurred and were felt to potentially affect the immunogenicity or safety results, then the above analyses were to be repeated for the PP population to assess the robustness of results.
• Planned analyses

Descriptive statistics were used to present all safety and immunogenicity results. 95% CIs were used for some immunogenicity criteria. Geometric means and 95% CIs were used for the log-transformed immunogenicity parameters. All analyses were performed with a significance level of 5% for two-sided tests and 2.5% for one-sided tests.

• A formal comparison of the immunogenicity results of the Enzira and Influsplit was not planned. However, summaries of immune responses were presented.

• **HI titers for the Co-primary endpoints:**
  o Please see the Statistical Review by Dr. Massie and section 8.1.2.1.5, Endpoints, above.
  o The number and percentage of the Evaluable Population with a minimum post-vaccination serum HI titer of 1:40 was calculated for each antigen strain and was assessed via a 97% one-sided binomial confidence interval.
  o The number and percentage of the Evaluable Population with an increase in HI antibody titer of at least 4-fold, with a minimum post-vaccination HI titer of 1:40 (ie, seroconversion), was calculated for each antigen strain, and was assessed via the 95% one-sided binomial confidence interval.

- **HI titers for the Secondary endpoints:**

  - Please see the Statistical Review by Dr. Massie and section 8.1.2.1.5, Endpoints, above.
  - The geometric mean of pre- and post- vaccination serum HI titers with 95% confidence intervals were calculated.
  - The number and percentage of the Evaluable Population with serum HI titer ≥ 1:40 post-vaccination was calcultated with exact 95% CIs. CPMP criteria for success were point estimate rates of > 60% for each antigen strain.
  - Seroconversion or Significant increase in the HI titer was calculated as the number and percentage of the Evaluable Population achieving an increase in post-vaccination serum HI titer of at least 4-fold, with a minimum post-vaccination titer of ≥ 1:40 along with 95% CI's. CPMP criteria for success were percent point estimate rates of > 30% for each antigen strain.
  - The geometric fold increase in HI titers was reported for each Study Vaccine along with 95% CIs.

Reviewer comment: The 95% CI appear to be calculated using the "exact" method. Please refer to the review from the Statistical Reviewer, Dr Massie.

- Secondary endpoints also included sub-population analyses of the effect of age, previous influenza vaccination, and pre-vaccination immune status on immune response.

Reviewer comment: The HI antibody test for this study did not contain an assay validation package. An assay validation was not requested for this study, in contrast to study CSLCT-FLU-05-09 that was designed for the basis of accelerated approval and used a validated HI antibody assay.

  - For studies CSLCT-FLU-05-09 and CSLCT-NHF-05-15, the HI assay was performed at----------. The applicant states that the assay was validated in accordance with ICH Guideline Q2B *Validation of Analytical Procedures: Methodology* and FDA Guidance for Industry *Bioanalytical Method Validation*. ----------' validation package for the HI assay specific to the 2006 Southern Hemisphere influenza vaccine and A/Hiroshima/52/2005 is provided in Module 5 Section 5.3.5.5 of the BLA.
  - For studies CSLCT-NHF-05-11, CSLCT-NHF-05-13, and CSLCT-NHF-04-99, the HI assay was performed by----------.

Reviewer comment: it is also important to note that the HI antibody assay validation procedures from ---------- that were submitted for review were felt to be adequate as determined by statistician Dr. Lev Sirota. Study CSLCT-NHF-05-15 used the same laboratory to perform this assay. Therefore, the immune response results from this study might carry more weight because the assay procedures from this lab are fully validated.

- **Safety analysis**

- Please see section 8.1.2.1.5, Endpoints, above.
- The number and rate of the type, frequency and intensity of solicited and unsolicited AEs compared to Influsplit.
- For local and systemic reactogenicity, the numbers and proportions of subjects experiencing these reactions were to be calculated along with exact 95% CIs. The differences in percentages (CSL IVV – Influsplit) with exact one-sided 97.5% upper confidence limits were to be calculated. CSL IVV would be considered no more reactogenic (non-inferior) if this upper confidence limit was ≤ 10%.
- AEs and SAEs were coded using MedDRA version 9.1.

• As noted in section 8.1.2.1.2, Design Overview, the planned sample size of n=400 was larger than the CPMP requirements for annual influenza strain variation studies in the EU to allow analysis of the effect of previous vaccination and high pre-vaccination titers on immune response. In addition, the comparator arm, Influsplit, n = 100, was included to allow assessment of the degree to which the observed outcomes were specific to CSL IVV.

• **Changes in the Planned Analyses**
- Difficulties in recruitment resulted in a total of 275 rather than the planned 400 participants
- There were no other significant changes

• **Protocol Deviations**
- There was one protocol violation in which subject #9009, Influsplit group, took a prohibited medication and was excluded from the Evaluable Population.
- There were no Protocol deviations.

8.1.2.2 Results of Study CSLCT-NHF-05-15

8.1.2.2.1 Populations enrolled and analyzed

- A total of 275 participants were enrolled and randomized to:
CSL IVV, n=206 or Influsplit, n=69.
- Safety population: all subjects who received Study Vaccine, n= 275.
CSL IVV n=206. Influsplit n=69.
Used for safety analysis.
- Evaluable Population: all subjects who received Study Vaccine, provided pre- and post-vaccination blood samples, and who were not excluded from analyses due to use of a prohibited medication. Any subject with an acute flu-like illness at any time during the study period was also excluded from the Evaluable Population.
CSL IVV n=206. Influsplit n=68.
Subject 9009 (Influsplit) excluded because of taking Leflunomide, prohibited, during the study.
Used for the immunogenicity analysis.
- All 275 subjects completed the study
- The applicant stated that recruitment ended December 8, 2006 because of difficulty in

recruiting subjects who had not already been vaccinated against influenza and after 275 participants received vaccine (safety population).

Table 8.1.2-4 Populations analyzed in Study CSLCT-NHF-05-15

Subject enrollment/ analysis			
	CSL IVV	**Influsplit**	**Total**
Subjects enrolled, n	206	69	275
Subjects not vaccinated	0	0	0
Subjects vaccinated	206	69	275
Subjects terminated	0	0	0
Protocol completed	206	69	275
Protocol violations	0	1	1
Protocol deviations	0	0	0
Safety Population	206	69	275
Evaluable Population	206	68	274

Reviewer comment: the applicant's population analysis was confirmed by review of the electronic datasets. All enrolled subjects completed the study, and there was only one protocol violation, no deviations. The Safety and Evaluable populations were essentially equal. No subjects were discontinued because of adverse events.

o The following demographic table is based on the Evaluable Population as presented in the applicant's submission, Table 2.1, Module 5, vol 14, and the data confirmed by the reviewer's evaluation of the datasets:

Table 8.1.2-5 Demographic Data and Other Baseline Characteristics Study CSLCT-NHF-05-15 (Evaluable Population)

Characteristic	CSL IVV n = 206	Influsplit n = 68	Total n = 274
Age (years) n Mean (SD) Median Min/max	 206 71.5 (5.26) 70.00 65.0/93.0	 68 71.1 (4.98) 70.00 65.0/84.0	 274
Gender Male Female	 103 103	 40 28	 143 131

Previous vaccination Against Influenza, n (%)	138 (67.0)	45 (65.2)	183 (66.8)
2002	148 (71.8)	45 (65.2)	193 (70.4)
2003	158 (76.7)	51 (73.9)	209 (76.3)
2004	180 (87.4)	57 (82.6)	237 (86.4)
2005			

Previous influenza illness n, (%) Yes No	33 (16.0) 173 (84.0)	12 (17.4) 57 (82.6)	45 (16.4) 230 (83.9)

Pre-vaccination titer ≥ 1:40 n, (%) H1N1 H3N2 B strain	119 (57.8) 179 (86.9) 66 (32.0)	39 (57.4) 57 (83.8) 23 (33.8)	158 (57.6) 236 (86.1) 89 (32.4)

Reviewer comment: The study was conducted at a single investigational site in the United Kingdom. Age, previous influenza vaccination, previous influenza illness, and pre-vaccination influenza titers ≥ 1:40 between CSL IVV and the comparator groups were very similar. There were proportionally more males than females in the Influsplit group, and equal number of males and females in the CSL IVV group.

- The electronic datasets confirmed that only one participant was taking a prohibited medication at baseline. The applicant reported that no participant had a significant medical condition which could potentially interfere with the study. Sixteen subjects had a concurrent diagnosis of asthma, 2 had hay fever, and 4 had history of migraine. There was a line listing of concomitant medical conditions in the line listing, but no general medical history included in the datasets.

- Race and ethnicity data was not collected for this study.

Table 8.1.2-6 Route of Administration CSL IVV versus Influsplit (based on review of the datasets), Evaluable Population

Route of Administration	CSL IVV® n, (%)	Influsplit® n, (%)
subcutaneous	206 (100.0)	6 (8.8)
intramuscular	0 (0.0)	62 (91.2)

Reviewer comment: It appeared that 100.0% of CSL IVV recipients received the study vaccine by deep subcutaneous injection while 91.2% of Influsplit recipients received the dose by intramuscular injection. At FDA's request, the applicant explained that deep subcutaneous injection was generally into the interstitial tissue just superficial to the deltoid muscle. The route of administration was not randomly assigned, but was selected on the basis of the subject's size and weight. CSL IVV was presented in a pre-filled syringe with 25 guage, 5/8 inch needle. Influsplit was presented in a pre-filled glass syringe with a plunger stopper and was injected with 25 guage, 5/8 inch needles. Investigational site staff were blinded, but staff delegated to administer the study vaccines were unblinded.

8.1.2.2.2 Efficacy endpoints and outcomes for CSLCT-NHF-05-15

o The applicants' summary of the efficacy data is based on text presented in Module 5 volume 13 pages 60-73 and in Tables 4.1-4.6 Module 5 volume 14, pp 116-126. The data are reproduced below from the applicant's data, and indicate that, for the Evaluable Population, CSL IVV met all three CPMP criteria for immunogenicity in older adults > 60 years of age for each influenza vaccine strain:

Criterion 1: the proportion of subjects achieving an increase in HI antibody titers of at least four-fold and a minimum post-vaccination HI titer of ≥ 1:40 should be > 30%;

Table 8.1.2-7 Proportion with post-vaccination four-fold increase in HI antibody titers, Older Adults ≥65 years of age, CSL IVV vs Influsplit, CSLCT-NHF-05-15

Strain	CSL IVV N=206	Influsplit N=68
H1N1 A/New Caledonia/20/99		
%	34.0	38.2
95% CI (%)	***27.5***, 40.9	***26.7***, 50.8
H3N2 A/Wisconsin/67/2005		
%	44.2	55.9
95% CI (%)	37.3, 51.2	43.3, 67.9
B Strain B/Malaysia/2506/2004		
%	45.6	39.7
95% CI (%)	38.7, 52.7	***28.0,*** 52.3

Reviewer comment: a prospective formal non-inferiority study of CSL IVV compared to Influsplit was not undertaken. Results between the two study vaccines were generally similar. Bold italics indicate where the more stringent FDA criteria using the lower bound of the 95% CI is <30%. This endpoint is not met for the H1N1 strain for either vaccine nor for B strain for Influsplit. However, the point estimates for both Study Vaccines meet the less stringent pre-specified CPMP immunogenicity criteria.

Criterion 2: the mean geometric increase in HI antibody titer should be > 2.0;

Table 8.1.2-8 Geometric Mean Fold Increase in HI titer, Older Adults ≥65, CSL IVV vs Influsplit, CSLCT-NHF-05-15

Strain	CSL IVV n = 206	Influsplit n = 68

H1N1		
GMFI	2.79	3.31
95% CI	2.417, 3.222	2.597, 4.210

H3N2		
GMFI	3.86	5.83
95% CI	3.226, 4.627	3.938, 8.638
B Strain		
GMFI	4.18	3.58
95% CI	3.536, 4.939	2.732, 4.680

GMFI=geometric mean fold increase

Reviewer comment: both CSL IVV and Influsplit met the pre-specified CPMP criteria for all three strains. The geometric mean fold increase is not a required immunogenicity endpoint in the FDA Guidance.

Criterion 3: the proportion of subjects achieving a HI antibody titer of ≥ 1:40 should be > 60%.

Table 8.1.2-9 Proportion of Older Adults ≥65 with post-vaccination HI titer of ≥ 1:40, CSL IVV vs Influsplit, CSLCT-NHF-05-15

Strain	CSL IVV n=206	Influsplit n=68
H1N1		
%	85.0	89.7
95% CI (%)	79.3, 89.5	79.9, 95.8
H3N2		
%	99.5	98.5
95% CI (%)	97.3, 100.0	92.1, 100.0
B Strain		
%	77.7	79.4
95% CI (%)	71.4, 83.2	67.9, 88.3

Reviewer comment: For the proportion of subjects achieving a HI titer ≥ 1:40, both point estimates and the lower bound of the 95% CI were > 60% for all three strains of influenza vaccine antigen in both the CSL IVV and Influsplit arms satisfying both CPMP and FDA criteria for immune response. The proportions were similar between study groups.

- **Immunogenicity conclusions**

CSL IVV met FDA criteria for the proportion of subjects with a four-fold increase in HI antibody titer and a post-vaccination HI antibody titer of ≥1:40

for H3N2 and B strains, but not for H1N1. However, the point estimate for this strain was 40.9 and the criteria for the proportion of subjects with a post-vaccination HI antibody titer greater than 1:40 was met for all three strains.

CSL IVV met all three CPMP criteria for immune response for all three strains in person's >65 years of age.

Similar immune response results were observed for the U.S. licensed vaccine, InfluSplit (equivalent to Fluarix).

The different routes of administration between CSL IVV and Influsplit do not appear to have adversely influenced the immunogenicity results.

Safety outcomes for CSLCT-NHF-05-15

• There were no deaths, SAEs, or discontinuations due to adverse events in this study. There were no flu-like illnesses.

• **Solicited Local Reactions**

Table 8.1.2-10 Vaccination Site Reactions CSL IVV vs Influsplit, Older Adults ≥65 years, CSLCT-NHF-05-15

Reaction	CSL IVV n= 206 n (%) E	Influsplit n= 69 n (%) E	Difference %CSL IVV – %Influsplit	95% CI
Pain				
Total	18 (8.7)	0	8.738	4.882,**12.594**
Mild	18	0		
Mod	18	0		
Severe	18	0		
	0	0		
	0	0		
	0	0		
	0	0		
Tenderness				
Total	69 (33.5)	12 (17.4)	16.104	5.080,**27.128**
Mild	69	12		
Mod	69 (33.5)	11		
Severe	69	11		
	5	1		
	5	1		
	0	0		
	0	0		

Erythema Total Mild Mod Severe	48 (23.3) 49 29 30 26 26 8 8	6 (8.7) 6 5 5 1 1 1 1	14.605	5.800,**23.410**
Induration Total Mild Mod Severe	21 (10.2) 21 17 17 8 8 0 0	2 (2.9) 2 2 2 0 0 0 0	7.296	1.574,**13.018**

Swelling Total Mild Mod Severe	 23 (11.2) 23 15 15 12 12 1 1	 0 0 0 0 0 0 0 0	11.165	6.864,**15.466**

Ecchymosis Total Mild Mod Severe	 9 (4.4) 9 6 6 3 3 1 1	 1 (1.4) 1 0 0 1 1 0 0	2.920	- 1.048,6.887

Reviewer comment: The table is based on Table 6.1 Mod 5 Vol 14 pp148-165 of the applicant's submission and was confirmed by reviewer evaluation of the electronic datasets. The applicant provided the "P-value" and 95% confidence intervals for difference in rates of reactogenicity. There were significantly more reactogenicity events in the CSL IVV group as compared to the Influsplit recipients. This might be related to the predominantly subcutaneous route of administration for the CSL IVV group. The sample sizes were small and, given the different routes of administration, it is difficult to make comparative safety conclusions. However, eight CSL IVV recipients (3.9%) experienced "severe" erythema. It is also difficult to directly compare these rates with those from the other studies submitted to the BLA because of differences in age groups, in parameters evaluated, and lack of severity grading. Please see Section 10 of this review, Overview of Safety across Trials.

- **Solicited Systemic Adverse Events through Post-Vaccination Day 4**

Table 8.1.2-11 Solicited Systemic AEs in Older Adults ≥65years, CSL IVV vs Influsplit, CSLCT-NHF-05-15

Reaction *	CSL IVV n=206 n (%) E	Influsplit n= 69 n (%) E	Difference %CSL IVV – %Influsplit	95% CI
Fever Total Mild Mod Severe	 2 (1.0) 2 0 0 2 2 0 0	 1 (1.4) 1 0 0 1 1 0 0	-0.478	-3.600,2.643
Headache Total Mild Mod Severe	 30 (14.6) 32 28 28 4	 7 (10.1) 8 6 6 3 4 0 0	4.418	- 4.181,**13.018**

	4 0 0			
Malaise Total Mild Mod Severe	20 (9.7) 22 19 21 3 3 0 0	5 (7.2) 5 5 5 1 1 0 0	2.462	-4.870,9.795

Myalgia Total Mild Mod Severe	29 (14.1) 32 29 32 2 2 0 0	7 (10.1) 7 7 7 1 1 0 0	3.933	- 4.629,**12.495**

Chills Total Mild Mod Severe	14 (6.8) 14 12 12 2 2 0 0		4 (5.8) 4 4 1 0	4 1 0	0.999	-5.498,7.496
Nausea Total Mild Mod Severe	7 (3.4) 6 1 0	7 6 1 0	2 (2.9) 2 0 0	2 2 0 0	0.500	-4.169,5.168
Vomiting Total	0	0	0	0	N/A	N/A

*If a subject had multiple events of the same intensity, they are counted only once in that intensity. Subjects/events may also be counted once if they had a single event of different severity on different days.

Reviewer comment: review of the electronic datasets confirmed the applicant's numbers. Overall, a greater percentage of CSL IVV recipients had systemic reactogenicity events than did Influsplit recipients, particularly headache, myalgia, and malaise. As noted above, differences in vaccine administration might be playing a role in the apparent differences in systemic reactogenicity. Although the applicant provided statistical parameters, the vast majority of these events were characterized as mild and only a few were moderate; none of the events were characterized as severe.

- **Unsolicited Adverse Events**

The table below lists unsolicited AEs by system organ class and preferred term, and is based on the applicant's Table 8.1, Module 5 Volume 14 Section 14.3.1 pp177-180.

Table 8.1.2-12 Unsolicited AEs occurring in at least 3% of subjects, Older Adults ≥65 years, CSL IVV versus Influsplit, CSLCT-NHF-05-15

System Organ Class/ Preferred term	CSL IVV n=206 % E	Influsplit n=69 % E

Respiratory, thoracic, and mediastinal ds	15.0	54	10.1	11
Nasal congestion	6.8	14	2.9	2
Rhinorrhea	5.3	11	5.8	5
Pharyngolaryngeal pain	4.9	12	2.9	2
Cough	5.3	11	1.4	1
Dry throat	1.0	2	0	0
Sneezing	1.0	2	0	0
Throat irritation	0.5	1	1.4	1
Asthma	0.5	1	0	0
Nervous system disorders	9.2	20	8.7	10
Headache	8.3	18	7.2	9
Dizziness	1.0	2	1.4	1

Gastrointestinal disorders	4.9	14	4.3	4
Diarrhea	1.5	3	0	0
Vomiting	1.0	2	1.4	1
Abdominal pain upper	0	0	2.9	2
Dyspepsia	1.0	2	0	0
Nausea	1.0	2	0	0
Toothache	0.5	1	1.4	1
Abdominal rigidity	0.5	1	0	0
Dry mouth	0.5	1	0	0
Hyperchlorhydria	0.5	1	0	0
Tongue ulceration	0.5	1	0	0
Musculoskeletal and connective tissue disorders	4.9	11	1.4	1
Back pain	1.9	4	0	0
Myalgia	1.5	3	0	0
Neck pain	0.5	1	1.4	0
Pain in extremity	1.0	2	0	0
Joint stiffness	0.5	1	0	0
Infections and infestations	3.4	8	1.4	1
Lower respiratory infection	1.5	3	1.4	1
Cystitis	0.5	1	0	0
Ear infection	0.5	1	0	0
Eye infection	0.5	1	0	0
Nasopharyngitis	0.5	1	0	0
Upper respiratory infection	0.5	1	0	0
General disorders and administration site conditions	2.4	5	2.9	3
Malaise	1.0	2	1.4	2
Chest discomfort	0.5	1	0	0
Chills	0.5	1	0	0
Fatigue	0.5	1	0	0
Injection site pain	0	0	1.4	1
Skin and subcutaneous tissue disorders	0.5	2	2.9	2
Eczema	0.5	1	1.4	1
Rash pruritic	0.5	1	1.4	1
Eye disorders	1.5	3	0	0
Lacrimation increased	1.0	2	0	0
Ocular hyperemia	0.5	1	0	0
Injury, poisoning, and procedural complications	1.0	2	1.4	1
Back injury	0	0	1.4	1
Chillblains	0.5	1	0	0
Joint sprain	0.5	1	0	0

Ear and labyrinth disorders	1.0	2	0	0
Ear pain	0.5	1	0	0
Motion sickness	0.5	1	0	0
Surgical and medical procedures	0.5	1	0	0
Tooth repair	0.5	1	0	0
Immune system disorders	0	0	1.4	1
Seasonal allergy	0	0	1.4	1

*Percentages are based on the number of subjects in each treatment group
E= total number of adverse events for the respective group

Reviewer Comment: the most common unsolicited AEs reported by CSL IVV recipients were headache, nasal congestion, rhinorrhea, pharyngolaryngeal pain, and cough. More subjects in the CSL IVV group experienced these events than in the Influsplit comparator group. Most unsolicited AEs were mild to moderate. There were no severe AEs related to CSL IVV. The applicant's data were confirmed by review of the electronic datasets. MedDRA terms for preferred term and SOCs were used in this evaluation.

8.1.2.3 Comments and Conclusions CSLCT-05-15

• The immunogenicity analysis suggests that CSL IVV met the FDA guidance criteria with a single exception of the lower bound of the 95% confidence intervals for the proportion with four-fold increase in HI antibody titer for strain H1N1 A/New Caledonia/20/99 that fell slightly below 30%. CSL IVV met the EMEA/CPMP criteria for success for all three strains.
• There is a potential flaw in the design of this study which may diminish its usefulness in support of this BLA: 100.0% of subjects received CSL IVV via the subcutaneous route while 91.2% of subjects received Influsplit by intramuscular administration. The deep subcutaneous route is an approved route of administration of influenza vaccine in the EU, and the injections in this study were all given in the region of the deltoid muscle. Although there are not sufficient data regarding subcutaneous or intradermal administration of influenza vaccine in the literature to suggest that these routes of administration are equivalent or noninferior to the traditional intramuscular route, there was no apparent difference in immunogenicity results related to the route of administration in this study. Therefore, despite the uncertain effect of the subcutaneous route of administration on immunogenicity, the immune responses elicited by CSL IVV in this study were overall acceptable and, in the reviewer's opinion, support licensure.

• Although this was not a comparative study with younger age groups, in general, the immune responses appeared to be lower among elderly subjects.

• The data suggest that the CSL IVV group experienced significantly greater local reactogenicity than the Influsplit group, most likely related to the subcutaneous route of administration.

• With respect to safety, the following conclusions can be made:
  - The most common solicited systemic reactions were headache, malaise, myalgia, and chills. CSL IVV recipients experienced more systemic reactions overall than did Influsplit recipients: 30.6% vs 15.9%. Despite this difference in reactogenicity, the majority of these symptoms were mild in intensity.
  - Solicited local reactions also occurred in a greater proportion of the CSL IVV group, 44.7% compared to 26.1% of the Influsplit group, and particularly for tenderness and erythema. The majority of reactions were mild in intensity with the exception of erythema which was characterized as severe in 8 (3.9%) CSL IVV recipients. The greater local and systemic reactogenicity reported by CSL IVV recipients may be related to the subcutaneous route of administration in 100% of the CSL IVV group compared to the intramuscular route of administration in 91.2% of the Influsplit group.
  - Unsolicited AEs were few, most commonly headache and upper respiratory symptoms, and were somewhat more common in the CSL IVV recipients.
  - There were no deaths, SAEs, or other significant AEs during the study.

• The results of study CSLCT-NHF-05-15 demonstrate satisfactory immune responses in Older Adults ≥65 years of age and do not raise significant or unexpected safety concerns. Overall, the data appear to have integrity and can be used to support approval of CSL IVV in the population of elderly adults greater than 65 years of age.

8.1.3 Trial # 3

8.1.3.1 Applicant's Protocol Number CSLCT-NHF-05-11

"A Randomised, Observer-Blind, Single-Centre Study to Evaluate the Safety, Tolerability and Immunogenicity of CSL IVV 2005/2006 Compared to Mutagrip® 2005/2006 in Healthy Adults ≥ 18 to < 60 years and in Healthy Older Adults Aged ≥ 60 years."

8.1.3.2.1 Objective/Rationale

• The primary objective was to demonstrate that the immune response following vaccination with CSL IVV 2005/2006 in healthy Adults aged ≥ 18 to < 60 years meets the criteria of the *CPMP/BWP/214/96 Note for Guidance.*

• The secondary objectives were:
  - To demonstrate that vaccination with CSL IVV™ 2005/2006 elicits a non-inferior immune response compared to vaccination with Mutagrip 2005/2006 in healthy Adults aged ≥ 18 to < 60 years and in healthy Older Adults aged ≥ 60 years using the criteria of the *CPMP/BWP/214/96 Note for Guidance.*
  - To demonstrate that CSL IVV 2005/2006 is no more reactogenic in healthy Adults aged ≥ 18 to < 60 years and in healthy Adults aged ≥ 60 years than Mutagrip 2005/2006 according to the criteria of the *CPMP/BWP/214/96 Note for Guidance.*

8.1.3.1.2 Design Overview:

• This was a Phase IV, randomized, observer-blind, comparator-controlled, single-center study which planned to enroll 400 healthy adults ≥18 years of age. Subjects were stratified according to age, and the number of participants planned for each group was:
    - Cohort A Adults: CSL IVV n=100, Mutagrip n=100
    - Cohort B Older Adults: CSL IVV n=100, Mutagrip n=100
• Within each cohort, subjects were randomized 1:1 to receive CSL IVV or Mutagrip at the Chiltern Clinical Research Unit in Slough, Berkshire, United Kingdom.
• The maximum study period for an individual participant was 21 ± 4 days from the administration of the Study Vaccine. Study Initiation Date (first participant visit) was October 6, 2005. Study Completion Date (last participant visit) was November 17, 2005.
• Each subject had blood drawn for pre-vaccination anti-HI antibody titers on Visit 1, Day 0, and was then vaccinated with a single 0.5mL 45mcg dose of trivalent influenza vaccine administered either by intramuscular or deep subcutaneous injection into the deltoid muscle of the arm. Subjects returned 21 ± 4 days later for an Exit Evaluation, between Day 17 and Day 25, which included post-vaccination anti-HI antibody titers and medical evaluation.
• Subjects experiencing signs/symptoms of an intercurrent flu-like illness at any time between vaccination Day 0 and Day 21 ± 4 were asked to return for medical evaluation and attempts to isolate virus from nasal wash/swabs within 3 days of onset of symptoms.
• The two Study Vaccines differed in physical appearance and were therefore administered by an unblinded staff member. All other investigational staff including the Principal Investigator as well as all participants were blinded.

8.1.3.1.3 Population

• The study planned to enroll 400 subjects ≥ 18 years of age. The actual vaccinated cohort consisted of:
    - CSL IVV n=206 (Adults n=102, Older Adults n=104)
    - Mutagrip n=200 (Adults n=102, Older Adults n=98)
• **Inclusion criteria:**
    - Healthy males or females, aged ≥ 18 years at the time of providing informed consent.
    - Provision of written informed consent to participate in the study and willingness to adhere to all protocol requirements.
    - Able to provide 20 mL of venous blood without undue distress/discomfort on two occasions.
    - Negative pregnancy test at enrollment before receiving study medication (female participants of child-bearing potential only). Those at risk of pregnancy during the study period must, in the opinion of the PI/delegate, have been taking/using adequate methods of contraception. Adequate methods were defined as:
        - Oral contraception
        - Intrauterine contraceptive device
        - Depot contraception (implants/injectables).
        - Abstinence

- Partner vasectomy.
- Condoms with spermicide.

- **Exclusion criteria:**
  - o Hypersensitivity to the active substances, to any of the excipients or to residues of the production process in either the Study Vaccine (eggs, egg protein, chicken protein, neomycin, polymixin, formaldehyde, or octoxinol 9).
  - o Influenza vaccination within the previous 6 months.
  - o Clinical signs of active infection and/or an oral temperature of ≥ 38°C at entry to the study. Study entry could have been deferred for such individuals, at the discretion of the PI/delegate.
  - o Immunosuppressive condition (including cancer), or a previously diagnosed (congenital or acquired) immunodeficiency disorder.
  - o Current (or within the 90 days prior to receiving the Study vaccine) immunosuppressive or immunomodulative therapy, including systemic corticosteroids, as follows:
    - Chronic or long-term corticosteroids: > 15 mg/day or oral prednisolone or equivalent daily.
    - Sporadic corticosteroids: > 40 mg/day of oral prednisolone or equivalent for more than two courses of > 14 days in the 3 months preceding vaccination.
    - Note: use of topical or inhaled corticosteroids prior to administration of the Study Vaccine or throughout the study was acceptable.
  - o Participation in a clinical trial or use of an investigational compound (i.e. a new chemical or biological entity not registered for clinical use) within 90 days prior to receiving the Study Vaccine or plans to enter a study during the study period.
  - o Known history of Guillain-Barre Syndrome (GBS).
  - o Active neurological disease.
  - o Current treatment with warfarin or other anticoagulant.
  - o Physical examination/medical history finding that the PI/delegate felt may affect the participant or study results.
  - o Evidence/history (within the previous 12 months) of drug or alcohol abuse.
  - o Unwillingness or inability to comply with the study Protocol.
  - o History of psychiatric disorders, which, in the opinion of the PI/delegate would have prevented participants from giving proper informed consent.

8.1.3.1.4 Products mandated by the protocol:

- **Table 8.1.3-1 Influenza vaccines used in trial CSLCT-NHF-05-11**

Cohort	Vaccine	Formulation	Market Authorization Number	Batch number
A	CSL IVV	Pre-filled syringe	PL 22236/0001	CTSLNHF0511
B	Mutagrip	Pre-filled syringe	PEI.H.00188.01.1	Z0590-2 and Z0591-1

• A single 0.5mL dose of trivalent influenza vaccine was administered by intramuscular or deep subcutaneous injection into the deltoid region of the upper arm contralateral to where the blood sample was collected when possible.
• Both vaccines were thimerosal-free
• Both vaccines consisted of split virion, inactivated influenza virus, propagated in hen's eggs, and contained the following three antigen strains recommended for the 2005/2006 Northern Hemisphere season by the CHMP BWP Ad hoc Influenza Working Group:

- 15 mcg A/New Caledonia/20/99 (H1N1)-like strain (A/New Caledonia/20/99 IVR-116)
- 15 mcg A/California/7/2004 (H3N2)-like strain (A/New York/55/2004 NYMC X-157)
- 15 mcg B/Shanghai/361/2002-like strain (B/Jiangsu/10/2003)

A total of 45 mcg of influenza hemagglutinin antigen.

8.1.3.1.5 Endpoints

• **Primary immunogenicity endpoints**

- Age-specific CPMP criteria for HI serology results and delineated in the *CPMP/BWP/214/96 Note for Guidance* were applied to each of the three vaccine strains.
- For each of the three vaccine strains, the proportion of vaccinees with a four-fold increase in anti-HI antibody titer and with a post-vaccination titer of at least ≥1:40 should be > 40% for participants aged ≥ 18 to < 60 years, and > 30% for participants aged ≥ 60 years.
- For each of the three vaccine strains, there should be a mean geometric increase > 2.5 for participants aged ≥ 18 to < 60 years, and > 2.0 for participants aged ≥ 60 years.
- For each of the three vaccine strains, the proportion of vaccinees with post-vaccination anti-HI antibody titers ≥ 1:40 should be > 70% for participants aged ≥ 18 to < 60 years, and > 60% for participants aged ≥ 60 years.

• **Secondary immunogenicity endpoints**

- A non-inferiority comparison of CSL IVV 2005/2006 and Mutagrip 2005/2006 based on the three *CPMP/BWP/214/96 Note for Guidance* criteria of seroconversion/significant increase, mean geometric increase, and proportion of participants with post-vaccination anti-HI antibody titers of ≥ 1:40 as described for the primary immunogenicity endpoints.

• **Safety endpoints**

o The primary safety endpoint was the proportion of subjects who experienced the following local or systemic reactions during the 4 days (Day 0 through Day 3) following vaccination:

Local vaccination site reactions: induration ≥ 50mm for > 3 days, erythema, pain, and ecchymosis.

Systemic reactions: temperature above 38ºC lasting longer than 24 hours, malaise, shivering.

The numbers and proportions of subjects with these reactions were calculated with 95% CIs for each treatment group. The difference in percentages between CSL IVV and Mutagrip was to be presented along with the exact one-sided 97.5% upper CI, and CSL IVV was to be considered non-inferior if the upper CI was ≤ 15%.

o Unsolicited AEs and SAEs were collected. Numbers and percentages of participants experiencing these events were tabulated according to vaccine group, age group, MedDRA system organ class and preferred term. Events were categorized according to intensity and relationship to study vaccine.

8.1.3.1.6 Surveillance/Monitoring

o Please refer to the schedule of procedures below (from the clinical study report):

Table 8.1.3-2 Study Procedures and Assessments

PROCEDURE	STAGE				
	PRE-STUDY	VISIT 1(DAY 0)	DAY 5 to DAY 9	EXIT EVALUATION (DAY 21 ± 4)	
Invitation to participate					
Informed consent procedure					
Medical history[A]					
Brief medical evaluation					
Physical evaluation[B]					
Temperature recorded					
Pre-vaccination serology sample obtained[C]					
Review of inclusion/exclusion criteria					

Administration of Study Vaccine[D]				
Diary card[E] completed by participants (Day 0 to Day 3)				
Diary card mailed to study site				
Diary card review and Adverse Event (AE) assessment				[F]
Post-vaccination serology sample obtained				
Collection of Serious Adverse Events (Day 1 to Day 21)				
Review of concomitant medication				
Nasal wash/swab for intercurrent flu-like illness[G]				

A: Including concomitant medication, previous influenza vaccination status, AEs to previous influenza vaccines and previous influenza illness.
B: If clinically indicated.
C: Haemagglutinin inhibition assay (HAI) and single radial haemolysis (SRH) assays (B strain only).
D: Participants randomised to receive either Enzira™ 2005/2006 or Mutagrip® 2005/2006 Study Vaccine.
E: 4-Day Solicited and Unsolicited AE diary card.
F: AE assessment only.
G: If applicable.

Source: Protocol (Appendix 16.1.1)

- Visit 1 (Day 0) – medical evaluation, physical exam if indicated, and phlebotomy for pre-vaccination anti-HI antibody titers followed by vaccination. Subjects were monitored for adverse reactions for 30 minutes post-vaccination.
- Diary cards were used to record solicited and unsolicited AEs during the 4 days following vaccination, Day 0 through Day 3.
- SAEs were recorded for the entire 21 ± 4 day study period.
- Intensity of unsolicited events were graded as:

Mild: Symptoms were easily tolerated and there was no interference with daily activities.

Moderate: Discomfort enough to cause some interference with daily activities.

Severe: Incapacitating with inability to do work or do usual activity.

- An SAE was defined as an 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 congenital anomaly/birth defect.

Was a Medically Significant Event: An event that was judged by the treating physician to potentially jeopardize the participant or required medication intervention to prevent one of the outcomes defined as an SAE.

o All AEs were recorded in the subject's CRF. All deaths and SAEs were reported to the Chiltern Pharmacovigilance Officer within 24 hours and then to the Independent Ethics Committee.

o Relationship to the study vaccine was categorized as:

Not related: In the PI/delegate's opinion, there was not a 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 the Study Vaccine administration and could not be reasonably explained by the known characteristics of the participant's clinical state.

Definitely: The AE followed a reasonable temporal sequence from the time of the Study Vaccine administration or reappeared when the Study Vaccine was re-introduced.

8.1.3.1.7 Statistical considerations

• Demographic and immunogenicity analyses were to be performed on the Evaluable Population. The safety analysis was to be performed on the Safety Population (see definitions under Populations).
• In addition to descriptive statistics used to present all safety and immunogenicity results, 95% CIs and geometric means were used to present immunogenicity results.
• The study vaccine was considered to be immunogenic for a particular strain if at least one of the three criteria set forth in the *CPMP/BWP/214/96 Guidance* was met (see Endpoints above).
• The difference in proportions and mean values between Mutagrip and CSL IVV were to be reported with a 97.5% one-sided upper CI. CSL IVV was considered to be non-inferior to Mutagrip if the upper CI for the difference (Mutagrip – CSL IVV) in the

proportion with anti-HI antibody titer and the seroconversion/significant increase rate did not exceed 20% and if the ratio of the geometric mean increase in HI titers did not exceed 2.0.
• CSL IVV was to be considered no more reactogenic than Mutagrip if the upper CI for the difference (CSL IVV – Mutagrip) for the proportion of subjects experiencing local and systemic reactions did not exceed 15%.
• Statistics were to be displayed by:
    o Mutagrip 2005/2006 Adult, Older Adult, and Overall
    o CSL IVV 2005/2006 Adult, Older Adult, and Overall
    o H1N1, H3N2, and B strains (for immunogenicity)
• Sample size
    o 400 participants were to be enrolled and stratified into two age cohorts:
        Cohort A=Healthy Adults aged ≥ 18 to < 60 years (n=200)
        Cohort B=Healthy Adults aged ≥ 60 years (n=200)
    o The two cohorts were further randomized in a 1:1 ratio to receive either CSL IVV or Mutagrip.
    o The applicant stated that the sample size of n=100 per arm for each cohort was selected in order to meet EU requirements for registration and also to demonstrate non-inferiority with the applicant's claim of a power of 90% per strain and age cohort.
• Changes in the protocol
    o The comparator vaccine was changed from Begrivac® (Chiron Behring GmbH & Co, Germany) and then to Fluarix™ (GSK) before changing to Mutagrip due to unavailability of the former vaccines.
    o There was a change in the designated serological testing laboratory from ----------
    ----

• Changes in the conduct of the study or in the planned statistical analyses
    o The database was unlocked once on December 20, 2005 and relocked on the same day because of subject 8144 (Adult, CSL IVV) having an AE of pain that was incorrectly recorded as "serious". This was corrected to "not serious".
    o The reporting of differences in the immunogenicity results between Mutagrip and CSL IVV was changed from reporting the exact 97.5% one-sided upper CI to asymptotic CIs. Please refer to the Statistical Review on this point.

8.1.3.2 Results of Study CSLCT-NHF-05-11

8.1.3.2.1 Populations enrolled and analyzed

• Two populations were defined for the analyses:

    o **Safety Population**: all participants who received a dose of Study Vaccine on Day 0. This population was used for the safety data analyses.

    o **Evaluable Population**: all participants who were vaccinated with Study Vaccines

on Day 0, provided both pre-and post-vaccination blood samples, and were not excluded because of:

Use of any investigational product during the study period
Administration of immunosuppressive/immunomodulative medication
Administration of any vaccine during the study period
Administration of immunoglobulins and/or any blood products during the study period
Occurrence of any confirmed or suspected immunosuppressive condition (including cancer), or immunodeficiency, including Human Immunodeficiency Virus (HIV) infection.

Table 8.1.3-3 Populations analyzed in Study CSLCT-NHF-05-11

Subject enrollment/ Analysis, n						
	CSL IVV, Adults	CSL IVV,Older	Total	Mutagrip,Adults	Mutagrip,Older	Total
Subjects Enrolled	102	104	206	102	98	200
Subjects vaccinated	102	104	206	102	98	200
Safety Population	102	104	206	102	98	200
Evaluable Population	102	104	206	102	98	200
Subjects Terminated/ Withdrawn	0	0	0	0	0	0
Protocol Completed	102	104	206	102	98	200
Protocol Violations	0	0	0	0	0	0
Protocol Deviations	0	1	1	2	1	3

Reviewer comment: All enrolled subjects completed the protocol. No subjects were terminated or withdrawn from the study. There were no protocol violations.

There were four protocol deviations. Three participants in the Mutagrip groups attended the Day 21 visit (post-vaccination titers) on Day 16, outside the ± 4 day window. Subjects 8171 and 8212, ages 33 and 44, were seroresponders and achieved a > 4-fold increase in GMT. Subject 9712, age 61, met criteria for H3N2 and B strain, but failed to serorespond or

achieve a 4-fold increase in GMT for H1N1. Subject 9692, age 72, was re-vaccinated 14 days after an unsuccessful attempt due to the needle becoming dislodged from the syringe. This subject had a seroresponse and 4-fold increase in GMT to the H3N2 antigen strain only.

Reviewer comment: CSL requested that these subjects be included in the Evaluable Population, and it does not appear that doing so has significantly changed the overall results of the study.

There was a protocol waiver for subject 9566, a 72 year old in the CSL IVV Older Adult cohort, who had trigeminal neuralgia and fulfilled exclusion criteria for active neurologic disease. This subject was receiving gabapentin on entry into study, but no adverse reactions or drug interactions were apparent.

The applicant's population analysis was confirmed by review of the electronic datasets.

Table 8.1.3-4 Demographics (Evaluable/Safety Population)

	CSL IVV			Mutagrip		
	Adults n = 102	Older Adults n = 104	Total n = 206	Adults n = 102	Older Adults n = 98	Total n = 200
Age (years) mean	42.41	67.36	55.01	43.02	67.90	55.21

Gender Male Female n (%)	39 (38.2) 63 (61.8)	62 (59.6) 42 (40.4)	101 (49) 105 (51)	32 (31.4) 70 (68.6)	41 (41.8) 57 (58.2)	73 (36.5) 127 (63.5)

Previous influenza vaccination 2001 2002 2003 2004 n (%)	13 (12.7) 21 (20.6) 21 (20.6) 18 (17.6)	44 (42.3) 57 (54.8) 65 (62.5) 66 (63.5)	57 (27.7) 78 (37.9) 86 (41.7) 84 (40.8)	20 (19.6) 15 (14.7) 25 (24.5) 19 (18.6)	46 (46.9) 49 (50.0) 56 (57.1) 64 (65.3)	66 (33.0) 64 (32.0) 81 (40.5) 83 (41.5)
Previous Influenza Illness Yes No n (%)	32 (31.4) 70 (68.6)	31 (29.8) 73 (70.2)	63 (30.6) 143(69.4)	42 (41.2) 60 (58.8)	30 (30.6) 68 (69.4)	72 (36.0) 128 (64.0)

Reviewer comment: The mean age between the CSL IVV and Mutagrip cohorts were similar. There was a greater proportion of females in both Adult cohorts and also in the Older Adult Mutagrip cohort. The history of prior influenza vaccination and previous influenza illness was generally similar between the two study vaccine groups.

The applicant's analysis was confirmed by evaluation of the electronic datasets. Review of the raw datasets appeared to confirm the applicant's analysis of demographic information, although mean ages could not be directly confirmed. The applicant did not collect data regarding race or ethnicity for this study. The study was conducted at the Chiltern research site for which this demographic data is supplied elsewhere in the BLA and which is summarized in Section 9.1.3 of this BLA review, and the area surrounding Chiltern is largely Caucasian.

General medical conditions were listed only. According to the applicant, no participant had significant medical history. No participant was taking prohibited medication. Evaluation of the electronic datasets revealed 21 subjects who used topical steroids which were permitted according to the protocol.

Route of Administration

Reviewer comment: In a June 29, 2007 response to an FDA request for information, the applicant explained that deep subcutaneous injection was generally into the interstitial tissue just superficial to the deltoid muscle. The route of administration was not randomly assigned, but was selected on the basis of the subject's size and weight. CSL IVV was presented in a pre-filled syringe with 25 guage, 5/8 inch needle. Mutagrip was presented in a pre-filled glass syringe with a plunger stopper and was injected with 25 guage, 5/8 inch needles. Investigational site staff were blinded, but staff delegated to administer the study vaccines were unblinded.

The applicant indicated that 404 subjects received study vaccine by the deep SQ route, none by the IM route, and that, for 2 subjects, the route of administration was unknown.

8.1.3.2.2 Efficacy endpoints and outcomes, summary of applicant's analyses

• The applicant provided the immunologic endpoints, point estimates with 95% CIs summarized in the table below:

Table 8.1.3-4 Immunologic endpoints study CSLCT-NHF-05-11, CSL IVV

	Adults 18 to<60 (n=102)		Older Adults ≥ 60 (n=104)	
H1N1 strain		EU		EU
% 4-fold increase in HI titer* (CI)	64.7 (54.6, 73.9)	>40%	49.0 >30% (39.1, 59.0)	
GMT fold Increase (CI)	10.47 (7.50, 14.63)	>2.5	4.68 >2.0 (3.62, 6.06)	
% with HI antibody titer ≥ 1:40 (CI)	87.3 >70% (79.2, 93.0)		63.5 >60% (**53.4**, 72.7)	
H3N2 strain				
% 4-fold increase in HI titer (CI)	93.1 (86.4, 97.2)	>40%	83.7 >30% (75.1, 90.2)	
GMT fold increase	30.96 >2.5 (24.13, 39.73)		14.63 >2.0 (11.04, 19.39)	
% with HI antibody titer ≥ 1:40	97.1 (91.6, 99.4)	>70%	88.5 >60% (80.7, 93.9)	
B strain				
% 4-fold increase in HI titer	62.7 (52.6, 72.1)	>40%	48.1 >30% (38.2, 58.1)	
GMT fold increase	7.98 (5.99, 10.63)	>2.5	4.72 >2.0 (3.64, 6.14)	
% with HI antibody titer ≥ 1:40	72.5 (**62.8**, 80.9)	>70%	70.2 >60% (60.4, 78.8)	

*% 4-fold increase in HI titer refers to the proportion with at least a four-fold increase in anti-HI antibody titer with a post-vaccination HI antibody titer of ≥1:40.

Bold print indicates where results would fail to meet FDA criteria for these parameters, although applying FDA criteria of the lower bound of the 95% confidence interval to adults ≥ 60 is not really valid as noted below.

Reviewer comment: CSL IVV met all three CPMP criteria for immune response for all three strains in both age groups. However, if FDA criteria for immune response are applied, B strain falls short of meeting the proportion with HI titer ≥ 1:40 in the Adult age group, and H1N1 also fails to meet this criterion in the older age group. The application of FDA criteria will be discussed further in the Summary of Clinical Efficacy across Trials section where a post hoc analysis of immunogenicity in adults ≥ 65 years of age will be presented.

The applicant provided a post hoc analysis of FDA criteria that the lower bound of the 95% confidence interval criteria for the proportion with a four-fold increase increase in HI antibody titer be >40% and the proportion with post-vaccination HI antibody titers ≥ 1:40 be >70% in the Adult age group < 65 years of age. These criteria were met for all three strains with the exception of the B strain where the proportion of post-vaccination HI antibody titers ≥ 1:40 was 62.8% in the CSL IVV group and 67.0% in the Mutagrip group. For adults ≥ 65, CSL IVV failed to meet criteria for proportion with four-fold increase in HI antibody titer and for proportion with HI titer ≥ 1: 40 for the H1N1 strain. The applicant noted, however, that the study was not powered to demonstrate compliance against the FDA criteria "The relatively small numbers of subjects in this study ≥ 65 years receiving both vaccines (60 per vaccine), contributes to the inability to demonstrate compliance with the FDA criteria due to the wide Confidence Intervals associated with small study numbers." Module 2 Volume 1 Section 2.5 p 39 Clinical Overview.

• Non-inferiority analysis
The immunogenicity results for Mutagrip presented by the applicant are summarized below:

Table 8.1.3-5 Immunologic endpoints study CSLCT-NHF-05-11, Mutagrip

	Adults 18 to<60 (n=102)		Older Adults ≥ 60 (n=104)
H1N1 strain		EU	EU
% 4-fold increase in HI titer (CI)	70.6 (60.7, 79.2)	>40%	40.8 >30% (31.0, 51.2)
GMT fold Increase (CI)	11.51 (8.44, 15.70)	>2.5	3.74 >2.0 (2.91, 4.82)

% with HI antibody titer ≥ 1:40 (CI)	89.2 >70% (81.5, 94.5)	***58.2*** >60% (**47.8**, 68.1)
H3N2 strain		
% 4-fold increase in HI titer (CI)	90.2 >40% (82.7, 95.2)	75.5 >30% (65.8, 83.6)
GMT fold increase	24.50 >2.5 (18.68, 32.14)	16.70 >2.0 (11.87, 23.49)

% with HI antibody titer ≥ 1:40	96.1 >70% (90.3, 98.9)	88.8 >60% (80.8, 94.3)
B strain		

% 4-fold increase in HI titer (CI)	62.7 >40% (52.6, 72.1)	44.9 >30% (34.8, 55.3)
GMT fold increase	8.48 >2.5 (6.44, 11.18)	4.47 >2.0 (3.37, 5.92)
% with HI antibody titer ≥ 1:40	76.5 >70% (**67.0**, 84.3)	***57.1*** >60% (**46.7,** 67.1)

Bold print=failed FDA criteria. Bold italics=failed CPMP criteria

In the Older Adult group, Mutagrip failed to meet CPMP criteria for the H1N1 and B strains for the proportion with anti-HI titer ≥1:40. As with CSL IVV, if FDA criteria for immune response are applied, B strain falls short of meeting the proportion with HI titer ≥ 1:40 in both age groups and H1N1 also fails to meet this criterion in the older age group. The application of FDA criteria will be discussed further in the Summary of Clinical Efficacy across Trials section where a post hoc analysis of immunogenicity in adults ≥ 65 years of age will be presented.

The applicant reported that CSL IVV was found to be non-inferior to Mutagrip by immune response criteria for each strain in both age groups for proportion with four-fold increase in HI antibody titer, ratios of geometric fold increase, and proportion with post-vaccination HI antibody titers ≥ 1:40. Please refer to the review from the Statistical Reviewer for further discussion of this analysis by the sponsor.

8.1.3.2.2 Safety outcomes for CSLCT-NHF-05-11

• There were no deaths, SAEs, serious AEs, or discontinuations due to AEs in this study.
• A summary of unsolicited AEs by intensity and causality, based on data presented by the applicant , Table 9, Mod 5 vol 17, Section 5.3.5.1-3, p 78 is as follows:

Table 8.1.3-6 Unsolicited AEs by Intensity and Causality, CSL IVV vs Mutagrip, CSLCT-NHF-05-11

	CSL IVV		Mutagrip	
	Adults ≥18to<60 N = 102 n (%)	OlderAdults ≥ 60 N = 104 n (%)	Adults ≥18to<60 N = 102 n (%)	Older Adults ≥60 N = 98 n (%)
Number of subjects with AE*	1 (1.0)	3 (2.9)	5 (4.9)	4 (4.1)

Number of vaccine-related AEs	1 (1.0)	1 (1.0)	2 (2.0)	2 (2.0)

AE intensity				
Mild	0	1 (1.0)	3 (2.9)	3 (3.1)
Mod	1 (1.0)	2 (1.9)	2 (2.0)	1 (1.0)
Severe	0	0	0	0
AE causality				
Definitely	0	0	1	1
Probably	0	0	0	1
Possibly	1	1	1	0
Unlikely	0	2	3	1
Not related	0	0	0	1

*****Multiple episodes of an AE counted only once for each subject

Reviewer comment: there were relatively few unsolicited AEs, none severe, and none definitely related to CSL IVV. The applicant's report was confirmed by review of the electronic datasets.

• Summary of local and general reactogenicity events based on the applicant's Tables 6.2 and 7.2 Mod 5 vol 17 is presented in the following table:

Table 8.1.3-7 Local and General Reactogenicity, CSL IVV versus Mutagrip, CSLCT-NHF-05-11

	CSL IVV		Mutagrip	
Reaction (all intensities)	Adults ≥18 to <60 n= 102 %	Older Adults ≥60 n = 104 %	Adults n =102 %	Older Adults n = 98 %
Induration > 50mm	0	1.0	1.0	3.1
Erythema	13.7	8.7	22.5	12.2
Ecchymosis	6.9	3.8	8.8	4.1
Pain	31.4	4.8	25.5	6.1
Fever ≥ 38°C	0	1.9	0	1.0
Malaise	1.0	0	0	0
Chills	0	0	0	0

Reviewer comment: The applicant's numbers were confirmed by review of the electronic datasets. CSL IVV recipients appeared to have slightly more pain and less erythema at the vaccination site than Mutagrip recipients, but otherwise had similar reactogenicity events. The applicant stated that the collection of data reflecting the intensity of solicited reactogenicity events is not a requirement of the CPMP, and these data were, therefore, not provided.

Summary of unsolicited adverse events based on the applicant's Tables 10, 8.4, and 9.1 Mod

5 vol 17 is presented in the following table:

Table 8.1.3-8 Unsolicited Adverse Events by System Organ Class and MedDRA Preferred Term, CSL IVV versus Mutagrip

	CSL IVV		Mutagrip	
System organ class/ Preferred term	Adults N=102 % E	Older Adults N=104 % E	Adults N=102 % E	Older Adults N=98 % E
Musculoskeletal Disorders	1.0 1	1.0 1	0 0	1.0 1
-Back pain				
-myalgia	0	1.0	0	0
-joint stiffness	0	1	0	0
	1.0	0	0	0
	1	0	0	0
	0	0	0	1.0
	0	0	0	1
Ear/labyrinth Disorders	0 0	1.0 1	0 0	0 0
-tinnitus				
	0	1.0	0	0
	0	1	0	0
Nervous system ds	0	1.0	1.0	1.0
-headache	0	1	1	1
	0	1.0	1.0	1.0
	0	1	1	1
Gastrointestinal ds	0	0	1.0	0
-glossodynia	0	0	1	0
	0	0	1.0	0
	0	0	1	0
General disorders/ Injection site cond	0 0	0 0	1.0 1	1.0 1
-inject site pain				
-inject site rcn	0	0	0	1.0
	0	0	0	1
	0	0	1.0	0
	0	0	1	0
Infections and Infestations	1.0 1	0 0	0 0	0 0
-respiratory tract infection	1.0	0	0	0
	1	0	0	0

Respiratory, thoracic and mediastinal ds -rhinnorhea -sneezing	0 0 0 0 0 0	0 0 0 0 0 0	1.0 1 0 0 1.0 1	1.0 1 1.0 1 0 0

Reviewer comment: There were only a total of 4 adverse events among 4 subjects in the CSL IVV group (4/206 = 1.9%) compared to a total of 9 subjects in the Mutagrip group (9/200 = 4.5%). Among CSL IVV recipients, 1 subject in the adult cohort and 3 subjects in the older adult cohort experienced unsolicited AEs. None of these were categorized as severe. The cases of tinnitus and rhinorrhea were felt unlikely to be related to the study vaccine. The applicant's summary was confirmed by review of the electronic datasets.

8.1.3.3 **Comments and Conclusions CSLCT-NHF-05-11**

o This study was not designed with a regulatory intent to support U.S. licensure of CSL IVV. The purpose of the study was to demonstrate that immune responses and safety observations following receipt of CSL IVV met criteria necessary for registration in the European Union for the 2005/2006 influenza season. The applicant compared safety and immune responses between the two treatment groups. The comparator vaccine, Mutagrip, is not approved for use in the U.S.

o Up to one third of CSL IVV recipients experienced local reactogenicity events. However, observed adverse events between subjects randomized to receive CSL IVV and Mutagrip were similar in number, and were no worse in older adults than in the <60 year age group. The applicant did not provide characterization of the adverse events by a toxicity grading scale for solicited AEs which limits the interpretability of the safety results. However, unsolicited AEs were very few in number and were mild to moderate in intensity. Overall, the safety data collected in this study appears satisfactory and similar to the safety profile found in the pivotal study CSLCT-FLU-05-09.

o Regarding immunogenicity, CSL IVV satisfied all three CPMP criteria for all three influenza antigen strains for immune response. If FDA criteria are applied to the age groups <60 and ≥60 as used in this study, CSL IVV met criteria for proportion with HI titer ≥ 1:40 except for the B strain in Adults and for the H1N1 strain in Older Adults. In the post hoc analysis of subjects ≥ 65 years of age, CSL IVV met criteria for proportion four-fold increase HI antibody titer and for proportion with HI titer ≥ 1:40 except for the H1N1 strain. This will be addressed further in the Summary of Clinical Efficacy across Trials. Although CSL IVV did not meet all FDA criteria, CSL IVV was found to be non-inferior to another trivalent inactivated influenza vaccine, Mutagrip, with respect to immune response parameters, according to the applicant's pre-specified analyses that were

not reviewed by FDA in advance of the study initiation.

o The collection of immune response data and unsolicited adverse events was similar to the collection of these parameters in the pivotal study and other studies submitted to support this BLA. Solicited general adverse events in this study were more limited than in CSLCT-NHF-05-09 and CSLCT-NHF-05-15. The applicant did not report the severity of solicited adverse events in this study which also limits the review of safety data.

o The usefulness of these data are further limited by the deep subcutaneous route of injection used to administer the study vaccines. With the exception of 2 subjects for whom the route of administration is unknown, all subjects received vaccination by the deep subcutaneous route in the area of the deltoid muscle. Although there is some data to support the use of both intradermal and subcutaneous administration of trivalent inactivated influenza vaccine, and although the deep subcutaneous route of administration of influenza vaccine is approved in the UK, the intramuscular route of administration is currently the only approved route in the US for trivalent inactivated influenza vaccines. Despite the uncertain effect of the subcutaneous route of administration on the immunogenicity, the immune responses elicited by CSL IVV in this study were overall acceptable and appeared to be similar to another trivalent inactivated influenza vaccine. In the reviewer's opinion, these data provide additional support for licensure.

o The small sample size also limits our ability to draw strong conclusions regarding safety and immune responses, but does provide some supportive evidence. For example, the safety data in this study did not raise any unexpected concerns. The results of this study support the overall conclusion that CSL IVV is safe and effective in young adults and in adults 65 years of age and older.

o There were no "intercurrent influenza-like illness" visits in this study.

8.1.4 Trial #4

8.1.4.1 Applicant's Protocol Number CSLCT-FLU-05-13

"A Single Site, Open-Label Study to Evaluate the Immunogenicity and Safety of CSL IVV in Healthy 'Adults' Aged ≥ 18 to < 60 years and in Healthy 'Older Adults' aged ≥ 60 years for the 2006/2007 Northern Hemisphere Influenza Season."

8.1.4.1.1 Objective/Rationale

• The primary objective of the study was to evaluate the immunogenicity of CSL IVV vaccine 2006/2007 in healthy 'Adults' aged ≥ 18 to < 60 years of age and in healthy

'Older Adults' aged ≥ 60 years of age according to the criteria of the *CPMP/BWP/214/96 'Note for Guidance'*.

• The secondary objectives of the study were to evaluate the safety of CSL IVV vaccine 2006/2007 in healthy 'Adults' aged ≥ 18 to < 60 years of age and in healthy 'Older Adults' aged ≥ 60 years of age through:

- The assessment of the frequency of solicited local reactions and general symptoms for 3 days following vaccination.
- The assessment of unsolicited adverse events of more than 2 days duration.

8.1.4.1.2 Design Overview

• This was a Phase IV, open-label, single site trial which planned to enroll up to 120 subjects stratified into two age groups: adults ≥ 18 to < 60 and older adults ≥ 60 years of age. Randomization and blinding were not applicable.
• The study was held at the Chiltern Clinical Research Unit in Slough, Berkshire, United Kingdom in the summer before the 2006-2007 influenza season. Subjects provided informed consent, underwent a medical evaluation, and provided pre-vaccination anti-HI antibody titers before receiving CSL IVV on Visit 1, study Day 0. Diary cards were issued for solicited AEs through Day 4 and for unsolicited AEs through Day 21. On Day 21 ± 4 days, subjects returned to the study site for Visit 2, review of AEs, medical evaluation if indicated, and for post-vaccination anti-HI antibody titers.
• An additional visit was scheduled for any subject who experienced an intercurrent influenza-like illness between Visits 1 and 2. If compatible with influenza, attempts were made to isolate virus by obtaining nasal swabs within 3 days of onset of symptoms.

8.1.4.1.3 Population

• The study planned to enroll up to 120 subjects ≥ 18 years of age. The actual vaccinated cohort consisted of 120 subjects:
- Adults ≥ 18 to < 60
- Older Adults ≥ 60

• **Inclusion criteria:**
- Healthy males or females, aged ≥ 18 years at the time of providing informed consent.
- Provision of written informed consent to participate in the study and willingness to adhere to all Protocol requirements.
- Were able to provide 20 mL of venous blood without undue distress/discomfort on two occasions.
- Negative pregnancy test at enrollment before receiving study medication (female participants of child-bearing potential only). Those at risk of pregnancy during the study period must, in the opinion of the PI/delegate, have been taking/using adequate methods of contraception. Adequate methods were defined as:

Oral contraception.

Intrauterine contraceptive device.

Depot contraception (implants/injectables).

Abstinence.

Partner vasectomy.

Condoms with spermicide.

- **Exclusion criteria:**
  - o Hypersensitivity to the active substances, to any of the excipients or to residues of the production process in the Study Vaccine (eggs, chicken protein, neomycin, polymyxin).
  - o Influenza vaccination within the previous 6 months.
  - o Clinical signs of active infection and/or an oral temperature of ≥ 38°C at entry to the study. Study entry could have been deferred for such individuals, at the discretion of the PI/delegate.
  - o Have a confirmed or suspected immunosuppressive condition (including cancer), or a previously diagnosed (congenital or acquired) immunodeficiency disorder.
  - o Current (or within the 90 days prior to receiving the Study Vaccine) immunosuppressive or immunomodulative therapy, including systemic corticosteroids, as follows:

    Chronic or long-term corticosteroids: > 15 mg/day of oral prednisolone or equivalent daily.

    Sporadic corticosteroids: > 40 mg/day or oral prednisolone or equivalent for more than two courses of > 14 days in the 3 months preceding vaccination.

  Note: Use of topical or inhaled corticosteroids prior to administration of the Study Vaccine or throughout the study was acceptable.
  - o Participation in a clinical trial or use of an investigational compound (i.e. a new chemical or biological entity not registered for clinical use) within 90 days prior to receiving the Study Vaccine or plans to enter a study during the study period.
  - o Vaccination with a registered vaccine within 30 days prior to receiving the Study Vaccine.
  - o Current treatment or treatment with cytotoxic drugs at any time during the 6 months prior to the administration of the Study Vaccine.
  - o Known history of Guillain-Barré Syndrome (GBS).
  - o Active neurological disease.
  - o Current treatment with warfarin or other anticoagulant.
  - o Physical examination/medical history finding that the PI/delegate felt may affect the participant or study results.
  - o Evidence/history (within the previous 12 months) of drug or alcohol abuse.
  - o Unwillingness or inability to comply with the study Protocol.

o History of psychiatric disorders, which, in the opinion of the PI/delegate would have prevented participants from giving proper informed consent.

8.1.4.1.4 Products mandated by the protocol:

• A single 0.5mL dose of trivalent influenza vaccine, CSL IVV 2006/2007 was administered by intramuscular or deep subcutaneous injection in the deltoid region of the arm, contralateral to where the pre-vaccination blood sample was drawn if possible.
• CSL IVV 2006/2007 was a split virion, inactivated influenza virus propagated in hen's eggs and contained the following three antigens recommended by the WHO for the 2006/2007 Northern Hemisphere influenza season:
- o 15 µg A/New Caledonia/20/99 (H1N1)-like strain;
- o 15 µg A/Wisconsin/67/2005 (H3N2)-like strain;
- o 15 µg B/Malaysia/2506/2004-like strain.

A total of 45 µg hemagglutinin antigen.
• The formulation was thimerosal-free and was presented in a pre-filled syringe.
• Batch number: CTSLNHF0513

8.1.4.1.5 Endpoints

• **Primary or Immunogenicity Endpoints** were based on the Evaluable Population for each vaccine antigen strain:
- o Number and percentage of evaluable participants with serum HI titre < 10 pre-vaccination (undetectable) and an increase in serum HI titre to ≥ 40 post-vaccination (called "seroconversion rate" by the applicant).
- o Number and percentage of evaluable participants with serum HI titre ≥ 10 pre-vaccination and a four-fold antibody titre increase post-vaccination ("significant increase" by the applicant).
- o Number and percentage of evaluable participants with seroconversions or significant increases in HI antibody titre and lower 95% confidence limit.
- o Fold increase in geometric mean titre and lower 95% confidence limit.
- o Number and percentage of evaluable participants with serum HI titre ≥ 40 post-vaccination and lower 95% confidence limit.
- o Criteria applied to the two age cohorts were based on the *CPMP/BWP/214/96 Note for Guidance on Harmonization of Requirments for Influenza Vaccines:*

Reviewer comment: FDA defines "seroconversion" as proportion four-fold increase in HI antibody titer and post-vaccination titer must be 1:40 or greater.

For vaccinees aged ≥ 18 to < 60 years, the criteria were as follows :

The number of seroconversions or significant increase in anti-haemagglutinin antibody titre (HI or SRH) should be > 40%;

The mean geometric increase should be > 2.5;

The proportion of participants achieving a HI titre ≥ 40 should be > 70%.

For vaccinees aged ≥ 60 years, the criteria are as follows:

The number of seroconversions or significant increase in anti-haemagglutinin antibody titre should be > 30%;

The mean geometric increase should be > 2.0;

The proportion of participants achieving a HI titre $\geq$ 40 should be > 60%.

• **Safety Endpoints**

o Local injection site and general reactogeniciy events from Day 0 through Day 3: induration larger than 50 mm diameter for 3 days, erythema, ecchymosis, pain, temperature above 38ºC for 24 hours or longer, shivering, malaise.

o AEs of more than 2 days duration and occurring from post-vaccination Day 0 through Day 3.

o All SAEs for the duration of the study period (21 days) for each subject.

o Intensity and causality for all AEs and SAEs.

8.1.4.1.6 Surveillance/Monitoring

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

Table 8.1.4-1 Study Procedures and Assessments

PROCEDURE	**STAGE**				
	PRE-STUDY	**VISIT 1 (DAY 0)**	**DAY 7 (±2 days)**	**EXIT EVALUATION (DAY 21 ± 4)**	
Invitation to participate					
Informed consent procedure					
Medical history					
Brief Medical Evaluation					
Physical examination		(if clinically indicated)			(if clinically indicated)
Temperature recorded					
Pre-vaccination serology sample obtained					
Review of Inclusion/Exclusion criteria					

Administration of Study Vaccine				
Diary card completed by participants (Day 0-3) including Temperature				
Diary card mailed to Study Site				
4-Day Solicited and Unsolicited Adverse Event Diary Card review and Adverse Event assessment				(Adverse Events assessment only)
Post vaccination serology sample obtained				
Collection of SAEs (Day 0 - Exit Evaluation)				
Review of concomitant medication				
Nasal swab for intercurrent flu-like illness*				

*If Applicable.

• Subjects received a pre-vaccination history, targeted physical if indicated, and completed a 4-day post-vaccination diary card for solicited and unsolicited AEs.

• All AEs of more than 2 days' duration and all SAEs were recorded in the subject's CRF.

• Intercurrent flu-like illness (ILI) was defined as oral temperature > 37.5ºC and at least one flu-like symptom: sore throat, cough, myalgia, chills, rigors, headache, or malaise. Subjects experiencing an ILI between Days 0 and Day 21 ± 4 were evaluated at the investigative site.

• The intensity/severity of Unsolicited AEs were graded as follows:

Mild: Symptoms were easily tolerated and there was no interference with daily activities.
Moderate: Discomfort enough to cause some interference with daily activities.

Severe: Incapacitating with inability to do work or do usual activity.

• An SAE was defined as an experience that:

- Resulted in death.
- Was life-threatening.

- Required unexpected in-patient hospitalisation or prolongation of existing hospitalisation.
- Resulted in persistent or significant disability/incapacity.
- Was congenital anomaly/birth defect.
- Was a Medically Significant Event: An event that was judged by the treating physician to potentially jeopardize the participant or required medication intervention to prevent one of the outcomes defined as an SAE.

• All SAEs were reported to the Chiltern Pharmacovigilance Officer within 24 hours, and, if vaccine-related, to the appropriate regulatory authority and the Independent Ethics Committee.

• All SAEs were to be followed until resolution or until the subject's condition stabilized.

• Relationship to the study vaccine was categorized as:

- Not related: In the PI/delegate's opinion, there was not a 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 the Study Vaccine administration and could not be reasonably explained by the known characteristics of the participant's clinical state.
- Definitely: The AE followed a reasonable temporal sequence from the time of the Study Vaccine administration or reappeared when the Study Vaccine was re-introduced.

8.1.4.1.7 Statistical considerations

• Populations analyzed
- Safety Population: all participants who received one dose of CSL IVV 2006/2007 on Day 0. This population was used for analysis of the safety data.
- Evaluable Population: all participants who were vaccinated with CSL IVV 2006/2007 on Day 0, provided both pre- and post-vaccination blood samples, did not have an intercurrent influenza-like illness, and were not excluded because of:
  - Use of any investigational product during the study period
  - Administration of immunosuppressive/immunomodulative medication
  - Administration of any vaccine during the study period
  - Administration of immunoglobulins and/or any blood products during the study period
  - Occurrence of any confirmed or suspected immunosuppressive condition (including cancer), or immunodeficiency, including Human Immunodeficiency Virus (HIV) infection.

• Demographic and immunogenicity analyses were performed on the Evaluable Population. Safety and demographic analyses were performed on the Safety Population.

• Descriptive statistics were to be used to present all safety and immunogenicity results. Ninety-five percent confidence intervals were used to present some immunogenicity data. Geometric means and 95% CIs for the log-transformed immunogenicity parameters. Please refer to Section 8.1.4.1.5 Immunogenicity and Safety Endpoints.

• Pre- and post-vaccination HI titers for each subject were performed simultaneously and in duplicate and expressed as the geometric mean of the two titers.

• AEs and SAEs were categorized according to the MedDRA preferred term and system organ class.

• The most frequent MedDRA preferred terms (≥ 5% events overall) and system organ class were to be presented.

• No interim analyses were planned

• Any HI result <10 (=undetectable) was expressed as 5.

• Sample size was based on the CPMP guidance requirements that there be a minimum of 50 participants in each age cohort.

• There were no Protocol amendments

• The database was unlocked once to amend a participant's data who had erroneously been recorded as having an ILI.

• Additional analyses: The immunogenicity data was also analyzed by pre-existing HI titers of <40 and ≥ 40.

8.1.4.2 Results of Study CSLCT-FLU-05-13

8.1.4.2.1 Populations enrolled and analyzed

• The first subject was vaccinated on May 30, 2006 (Study Initiation Date), and the last on June 23, 2006 (Study Completion Date). The maximum active study time for each subject was 21 ± 4 days from administration of the Study Vaccine.

The following table is based on the applicant's Table 2, p 46, Module 5, Volume 22:

Table 8.1.4-2 Participant Disposition Study CSLCT-FLU-05-13

	Adult n (%)	Older Adult n (%)
Total enrolled	Vaccine-related included possibly, probably, or definitely	

Protocol deviations/ withdrawals	1 (1.7%)	0
Reason for withdrawal SAE AE Protocol violation Withdrew consent Lost to follow-up Death Other	 0 0 0 0 1 (1.7%) 0 0	 0 0 0 0 0 0 0

Reviewer comment: Only one subject failed to complete the protocol. No participant was withdrawn because of death, SAEs, or AEs. The applicant's data was confirmed by interrogation of the datasets.

The table below is based on the applicant's Tables 2.2, 3, and 4.1, Module 5, vol 22, and presents demographic characteristics of subjects in Study CSLCT-NHF-05-13:

Table 8.1.4-5 Demographic Data and Other Baseline Characterisitics
Study CSLCT-FLU-05-13 (Safety Population)

Characteristic	Adult (n=60)	Older Adult (n=60)
Age (years) mean (SD)	 40.67 (12.402)	 66.93 (4.618)
Gender n (%) male female	 21 (35.0) 39 (65.0)	 33 (55.0) 27 (45.0)
Previous influenza vaccination 2002 2003 2004	 5 (8.3) 10 (16.7) 16 (26.7)	 28 (46.7) 33 (55.0) 47 (78.3)

2005	34 (56.7)	60 (100.0)
Previous influenza illness		
Yes	13 (21.7)	20 (33.3)
No	47 (78.3)	40 (66.7)

Pre-vaccination ≥ 1:40 n (%) (Evaluable Population)		
H1N1	29 (49.2)	17 (28.3)
H3N2	37 (62.7)	45 (75.0)
B strain	8 (13.6)	14 (23.3)

Reviewer comment: The study was conducted at a single investigational site in the United

Kingdom. No specific data regarding race or ethnicity was provided for this study, but the demographics for the Chiltern research site were primarily Caucasian. The mean age in the Adult group was 40.67 and in the Older Adult group 66.93. There was a greater percentage of females in the Adult cohort and relatively fewer females in the Older Adult group. While only 8.3 to 56.7% of younger Adults had received influenza vaccine in the four years prior to the study, the majority of Older Adults had been previously vaccinated. The majority of subjects in the two groups did not report previous influenza illness. A substantial number of younger Adults had evidence of anti-HI antibody titers ≥ 1:40 for H1N1 and H3N2 prior to vaccination, whereas Older Adults demonstrated significant pre-vaccination titers to the H3N2 strain only.

General medical history and concomitant medications were listed in the applicant's submission. No subject was taking prohibited medications including immunosuppressive agents.

Route of Administration
Reviewer comment: In a June 29, 2007 response to an FDA request for information, the applicant explained that deep subcutaneous injection was generally into the interstitial tissue just superficial to the deltoid muscle. The route of administration was not randomly assigned, but was selected on the basis of the subject's size and weight. The applicant indicated that for this study 23 subjects received the CSL vaccine by deep subcutaneous route and 97 by intramuscular injection.

8.1.4.2.2 Efficacy endpoints for CSLCT-NHF-05-13

- A summary of the applicant's data appears in the table below and is based on Tables 4, 5, and 6, Module 5, vol 22, pp57-61, and Tables 4.10- 4.12 Module 5 Vol 22, Section 5.3.5.2-1, pp 115-123. For each cohort, the subpopulation of subjects with pre-vaccination anti-HI antibody titers < 1:40 was also evaluated.

Table 8.1.4-6 Immunogenicity endpoints Study CSLCT-NHF-05-13, 21 days following administration of CSL IVV

Strain/ criterion	Adults		Older Adults	
	Total cohort n=59	Pre-vaccination HI<1:40	Total cohort n=60	Pre-vaccination HI<1:40
H1N1				

%4-fold increase in HI titer (CI)	***39.0*** **26.5,** 52.6	66.7 47.2, 82.7	***8.3*** **2.8**, 18.4	***11.6*** **3.9,** 25.1
GMT fold Increase	4.25	9.89	***1.83***	2.19

% with HI titer ≥1:40 (CI)	91.5 81.3, 97.2	83.3 **65.3,** 94.4	***58.3*** **44.9,** 70.9	***41.9*** **27.0,** 57.9
H3N2				
%4-fold increase in HI titer (CI)	45.8 **32.7,** 59.2	77.3 54.6, 92.2	***30.0*** **18.8,** 43.2	86.7 59.5, 98.3
GMT fold Increase	4.53	12.88	2.66	12.18
% with HI titer ≥1:40 (CI)	94.9 85.9, 98.9	86.4 **65.1,** 97.1	100.0 94.0, 100.0	100.0 78.2, 100.0
B strain				
% 4-fold increase in HI titer (CI)	54.2 40.8, 67.3	62.7 48.1, 75.9	36.7 **24.6,** 50.1	45.7 30.9, 61.0
GMT fold increase	6.44	7.89	3.25	4.10
% with HI titer ≥1:40 (CI)	71.2 **57.9,** 82.2	66.7 **52.1,** 79.2	61.7 **48.2,** 73.9	***50.0*** **34.9,** 65.1

Bold print indicates failure to meet FDA criteria for immune response.
Bold italics indicate failure to meet CPMP criteria for immune response.

Reviewer comment: For the Adult group, CSL IVV met CPMP criteria for immune response for all three vaccine antigen strains. For the Older Adult group, CSL IVV met CPMP criteria for the B strain (by GMT fold increase) and for H3N2 strain (by % with HI titer ≥1:40 and GMT fold increase), but did not meet CPMP criteria for H1N1 strain. However, the GMT fold increase was greater than 2.0 for the subpopulation with pre-vaccination titers ≤1:40, which allowed CPMP approval.

The immune response results in the Adult group did not meet FDA criteria for some of the antigens, including the % 4-fold increase for H1N1 and H3N2 as well as % with HI titer ≥1:40 for the B strain. CSL IVV clearly failed the more stringent FDA criteria in five of the six immune response endpoints in the Older Adult group; only the % with HI titer ≥1:40 for the H3N2 strain was met. Immune responses in the geriatric population were low in this study.

8.1.4.2.3 Safety outcomes for CSLCT-NHF-05-13

- There were no deaths, SAEs, or discontinuations due to AEs in this study, and no intercurrent influenza-like illnesses.
- Solicited local and general reactions are presented in the table below and are derived from the applicant's Tables 7.1, 6.1, and 6.2

Table 8.1.4-7 Solicited General and Local Reactogenicity Events CSLCT-NHF-05-13

Solicited general and local reactogenicity events	Adult (n=60) %	E	Older Adult (n=60) %	E
Fever >38°C ≥24hr	0	0	0	0
Shivering	3.3	2	1.7	1
Malaise	8.3	5	0	0
Induration >50mm>3days	1.7	1	1.7	1
Erythema	21.7	13	16.7	10
Ecchymosis	8.3	5	8.3	5
Pain	35.0	22	23.3	14

%=percent of subjects experiencing the event
E=total number of events

Reviewer comment: Review of the electronic datasets confirmed the local and general reactogenicity events reported by the applicant. The collection of general reactogenicity events was more limited than in the pivotal study CSLCT-FLU-05-09 and non-IND study CSLCT-NHF-05-15, but very similar to that for the other two non-IND supporting studies.

- **Unsolicited Adverse Events**

The applicant's reports of unsolicited AEs are summarized in the tables below (based on applicant's Table 8.1 and 9.1 Mod 5 Vol 22 Sect 5.3.5.2-1, pp145,149-150.)

Table 8.1.4-8 Unsolicited Adverse Event Intensity and causality CSL-NHF-05-13

	Adult (n=60) n (%) *	Older Adult (n=60) n (%)
# of Adverse Events	8 (13.3)	2 (3.3)
# of related AEs	0	0
AE intensity		
Mild	2 (3.3)	1 (1.7)
Moderate	5 (8.3)	1 (1.7)
Severe	1 (1.7)	0
AE causality		
Definitely related	0	0
Probably related	0	0
Possibly related	0	0
Unlikely related	4 (6.7)	
Not related	4 (6.7)	2
		0

*Percentages based on number of subjects experiencing an AE within a treatment group.

Table 8.1.4-9 Unsolicited AEs by system organ class and preferred term CSLCT-NHF-05-13

System organ class/ Preferred term	Adult (n=60) %	Older Adult (n=60) %
Number of Adverse Events	13.3	3.3
Infections and infestations	3.3	1.7
Upper respiratory tract Infection	3.3	1.7
Musculoskeletal/connective Tissue disorders	3.3	0
Back pain	1.7	0
Periarthritis	1.7	0
Nervous system disorders	1.7	1.7
Headache	0	1.7
Migraine	1.7	0
Ear and labyrinth disorders	1.7	0
Ear pain	1.7	0
Injury poisoning and procedural complications	1.7	0
Arthropod bite	1.7	0
Skin and subcutaneous tissue disorders	1.7	0
Rash erythematous	1.7	0

*Percentages based on number of subjects experiencing an AE

Table 8.1.4-10 Most frequent adverse events by preferred term (>5%events) CSLCT-NHF-05-13

Preferred term	Adult (n=60) n	(%)*	Older Adult (n=60) n	(%)
# of adverse events	8		2	
Upper respiratory tract infection	2	(25.0)	1	(50.0)
Arthropod bite	1	(12.5)	0	
Back pain	1	(12.5)	0	
Ear pain	1	(12.5)	0	
Headache	0		1	(50.0)
Migraine	1	(12.5)	0	
Periarthritis	1	(12.5)	0	
Rash erythematous	1	(12.5)	0	

*percentages based on number of subjects experiencing an AE

Reviewer comment: Overall the incidence of unsolicited adverse events in this study was low, 8 (13.3%) of Adult participants and 2 (3.3%) of Older Adult participants experiencing at least one AE. The majority were mild or moderate in intensity, and none were considered likely to be vaccine-related. Subject #8025, a 53 year old Adult, experienced severe periarthritis or frozen shoulder that was judged by the investigator to be unrelated to CSL IVV. The most frequent AEs were two upper respiratory tract infections, considered not vaccine-related.

Evaluation of the electronic datasets by the Medical Reviewer revealed results identical to the applicant's summary.

Overall, CSL IVV appeared to demonstrate a reasonable safety profile in study CSL-NHF-05-13.

8.1.4.3 Comments and Conclusions Study CSL-NHF-05-13

• This study was not designed with a regulatory intent to support U.S. licensure of CSL IVV. The purpose of the study was to evaluate the immunogenicity and safety of the trivalent 2006/2007 formulation of CSL IVV in order to maintain licensure in the European Union.

• In the Adult group, the mean age was 40.67 years and 56.7% of subjects had a history of previous influenza vaccination. The results from this group met EMEA *CPMP/BWP/214/* criteria for immune response. However, some immune response endpoints would not have fulfilled FDA criteria. For example, the lower bound of the 95% CI of H1N1 and H3N2 strains was below 40% for proportion with four-fold increase in HI titer, and the lower bound of the 95% CI of the B strain was below70% for proportion of subjects with a post-vaccination anti-HI titer of ≥ 1:40.

• In the Older Adult group, the mean age was 66.93 years, and 100% of subjects had a history of previous influenza vaccination. The H1N1 strain did not meet CPMP criteria for immune response. The fact that 100% of this group had received influenza vaccine the previous year was felt by the applicant to be a possible factor influencing the suboptimal response, and the subpopulation of those participants with a pre-vaccination anti-HI antibody titer of < 1:40 was, therefore, analyzed further. The criterion for > 2.0 fold increase in GMT was met in this subgroup, but the sample size was 43 participants, smaller than the size of 50 suggested by the CPMP, and the other criteria were still not achieved. For the older adult group, five out of the six FDA criteria for acceptable lower bound of the 95% confidence intervals of immune responses would not have been achieved.

• Although there is concern about the lower immune responses observed in this study, it is difficult to draw strong conclusions from the results of one study conducted in a small population at a single study site using influenza vaccine from one particular season. In

addition, the route of administration was apparently more often intramuscular in this study, in contrast to deep subcutaneous administration in other non-US IND studies.

• As in the other non-IND studies submitted to the BLA, interpretation of the immunogenicity data is limited by the small sample size and by the uncertain impact of the deep subcutaneous route of administration in 19.1% of subjects. In addition, the performance of the unvalidated HI assays at a laboratory different from that used in studies CSLCT-FLU-05-09 and CSLCT-NHF-05-15 makes direct comparison of the immunogenicity results less reliable than if the assays had been performed at the same laboratory.

• Regarding safety, CSL IVV demonstrated expected local and systemic reactogenicity that did not differ significantly between the Adult and Older Adult groups. There were no deaths, SAEs, severe vaccine-related AEs, or discontinuations due to unsolicited AEs.

• There were no "intercurrent influenza-like illness visits" in this study.

8.1.5 Trial #5

8.1.5.1 Applicant's Protocol Number CSLCT-NHF-04-99

"A Single Site, Open-label Study to Evaluate the Immunogenicity and Safety of CSL IVV in Healthy Adults aged ≥ 18 to < 60 years in Healthy Older Adults aged ≥ 60 years for the 2005 Northern Hemisphere Influenza Season."

8.1.5.1.1 Objective/Rationale

• The primary objective was to evaluate the immunogenicity of CSL IVV in healthy Adults aged ≥ 18 to < 60 years and in healthy Older Adults aged ≥ 60 years of age according to the criteria of the CPMP/BWP/214/96 guideline. The study was conducted to evaluate the new strains incorporated into the vaccine to satisfy annual requirements for registration and marketing in the European Union.

• The secondary objectives were to evaluate the safety of CSL IVV in healthy Adults aged ≥ 18 to < 60 years of age and in healthy Older Adults aged ≥ 60 years of age through:

- The assessment of the frequency of Solicited local and general symptoms for 3 days following vaccination.
- The assessment of Unsolicited Adverse Events (AEs) of more than 2 days

duration.

8.1.4.1.2 Design Overview

• This was a Phase III, open-label, single site trial which planned to enroll 60 healthy Adults aged ≥ 18 and < 60 years of age and 60 healthy Older Adults ≥ 60 years of age for the 2005 Northern Hemisphere influenza season. Randomization and blinding were not applicable.

• The study was held at the Chiltern Clinical Research Unit in Slough, Berkshire, United Kingdom. The first subject was vaccinated on May 31, 2005 (Study Initiation Date), and the last subject was vaccinated on June 25, 2005 (Study Completion Date). The maximum time "on-study" for an individual participant was 21 ± 4 days from administration of the study vaccine. The maximum duration of time for a participant "off-study" was 4 to 6 months post-vaccination.

• There were 3 on-site study visits and one Intercurrent Flu-like Visit (if applicable).

- o Visit 1, Day 0: informed consent, medical evaluation, pre-vaccination serology, administration of study vaccine, issuing of diary cards
- o Day 7 Diary cards reviewed, all AEs entered into CRF
- o Exit Evaluation Visit (2), Day 21 ± 4 days: post-vaccination serology and brief medical evaluation
- o Off Study Visit (3), 4 to 6 months post-vaccination: post-vaccination serology
- o Intercurrent Flu-Like Illness Visit: for participants with signs/symptoms of a flu-like illness between vaccination and exit evaluation visit. If symptoms confirmed by medical evaluation, nasal swab for viral isolation within 3 days on onset of symptoms.

8.1.5.1.2 Population

• 120 subjects were enrolled:

- o 60 healthy Adults ≥ 18 to < 60 years of age
- o 60 healthy Older Adults ≥ 60 years of age

• **Inclusion Criteria**

Participants were included in the study providing they met the following criteria:

- o Healthy males or females aged ≥ 18 years at the time of providing informed consent.
- o Provision of written informed consent to participate in the study and willingness to adhere to all Protocol requirements.
- o Be able to provide a sample of up to 10 mL of venous blood without undue distress/discomfort.
- o Negative pregnancy test at enrolment before receiving study medication (female participants of child-bearing potential only). Those at risk of pregnancy during the study period must in the opinion of the PI/delegate, be taking/using

adequate methods of contraception. Adequate methods are defined as:

Oral contraceptive.

Intrauterine contraceptive device.

Depot contraceptive (implants/injectables).

Abstinence.

Partner vasectomy.

Condoms with spermicide.

• **Exclusion Criteria**

Participants were excluded from the study for any of the following reasons:

o Known allergy to eggs, chicken feathers, neomycin, polymyxin or any other components of the vaccine.

o Influenza vaccination within the previous 6 months.

o Clinical signs of active infection and/or an oral temperature of ≥ 38°C at study entry. Study entry could have been deferred for such individuals, at the discretion of the PI/delegate.

o Have a confirmed or suspected immunosuppressive condition (including cancer), or a previously diagnosed (congenital or acquired) immunodeficiency disorder.

o Current (or within the 90 days prior to receiving the study vaccine) immunosuppressive or immunomodulative therapy, including systemic corticosteroids, as follows:

Chronic or long term corticosteroids > 15 mg/day of oral prednisolone or equivalent daily.

Sporadic corticosteroids > 40 mg/day or oral prednisolone or equivalent for more than two courses of > 14 days in the 3 months preceding vaccination.

Note: Use of topical or inhalant corticosteroids prior to administration of the study vaccine or throughout the study was acceptable.

o Participation in a clinical trial or use of an investigational compound (i.e. a new chemical or biological entity not registered for clinical use) within 90 days prior to receiving the study vaccine or plans to enter a study during the study period.

o Vaccination with a registered vaccine within 30 days prior to receiving the study vaccine.

o Current treatment or treatment with cytotoxic drugs at any time during the 6 months prior to administration of the study vaccine.

o Known history of Guillain-Barré Syndrome (GBS)[3,4].

o Physical/medical history that the PI feels may affect the participant or study results.

o History of neurological disorders.

- Evidence or history (within the previous 12 months) of drug or alcohol abuse.
- Unwillingness or inability to comply with the Study Protocol.
- History of psychiatric disorders, which, in the opinion of the PI would have prevented participants from giving proper informed consent.

8.1.5.1.4 Products mandated by the protocol:

• A single 0.5mL dose of trivalent influenza vaccine, (CSL Limited), was administered by intramuscular or deep subcutaneous injection in the deltoid region of the arm, contralateral to where the pre-vaccination blood sample was drawn if possible.

• The study vaccine contained the following three influenza antigen strains recommended by the WHO for the 2005/2006 Northern Hemisphere influenza season:

- 15 μg A/New Caledonia/20/99 (H1N1)-like strain
  (A/Caledonia/20/99strain)
- 15 μg A/California/7/2004 (H3N2)-like strain
  (A/New York/55/2004strain)
- 15 μg B/Shanghai/361/2002-like strain
  (B/Jiangsu/10/2003strain).

A total of 45 μg hemagglutinin antigen.

• The formulation was thimerosal-free and was presented in a pre-filled syringe.

• Batch number: CTSLNHF0499B.

Route of Administration

Reviewer comment: In a June 29, 2007 response to an FDA request for information, the applicant explained that deep subcutaneous injection was generally into the interstitial tissue just superficial to the deltoid muscle. The route of administration was not randomly assigned, but was selected on the basis of the subject's size and weight. The applicant indicated that for this study all 120 subjects received the CSL vaccine by deep subcutaneous route.

8.1.5.1.5 Endpoints

• **Primary or Immunogenicity Endpoints** were assessed in the Evaluable Population for each vaccine strain:

- Number and percentage of participants with serum HI titer < 10 pre-vaccination and an increase in serum HI titer to ≥ 40 post-vaccination (seroconversion rate).
- Number and percentage of participants with serum HI titer ≥ 10 pre-vaccination and a four-fold antibody titer increase post-vaccination (significant increase).
- Number and percentage of participants with seroconversions or significant increases in HI antibody titer and lower 95% confidence limit.
- Fold increase in geometric mean titer and lower 95% confidence limit.
- Number and percentage of participants with serum HI titer ≥ 40 post-vaccination and lower 95% confidence limit.

o Criteria for determination of immune response were based on the *CPMP/BWP/214/96 Guidance* and were as follows:

For vaccines ≥ 18 to < 60 years of age:

the number of seroconversions or significant increase in anti-HI titer should be >40%;

The mean geometric increase should be > 2.5;

The proportion of participants achieving a HI titer ≥ 40 should be > 70%.

For vaccines ≥ 60 years of age:

The number of seroconversions or significant increase in anti-HI titer should be > 30%;

The mean geometric increase should be > 2.0;

The proportion of participants achieving a HI titer ≥ 40 should be > 60%.

According to the *CPMP/BWP/214/96 guidance* document at least one of the above criteria should be met by each of the three vaccine strains.

Reviewer comment: although the applicant refers to "seroconversion" and "significant increase" this reviewer will focus on the immune response endpoint of the proportion with four-fold increase in HI antibody titer, with a post vaccination HI antibody titer to be at least 1:40.

• **Safety Endpoints**

o Solicited local injection site and general reactogenicity events from Day 0 through Day 3: induration > 50mm for 3 days, erythema, ecchymosis, pain, temperature above 38°C for 24 hours or longer, chills, and malaise. Assessed by age group and causality.

o Unsolicited AEs of two or more days' duration, Day 0 through Day 3.

o All SAEs for each subject for the entire study duration (21 days).

o Intensity and causality for all AEs and SAEs.

8.1.5.1.6 Surveillance/Monitoring

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

Table 8.1.5-1 Schedule of Study Procedures and Assessments

PROCEDURE	**STAGE**				

	PRE-STUDY	VISIT 1 (DAY 0)	DAY 5-DAY 9	EXIT EVALUATION VISIT (DAY 21 ± 4)	4-6 MONTH FOLLOW-UP SEROLOGYVISIT	
Invitation to participate						
Informed consent procedure						
Medical history [A]						
Brief medical evaluation						
Physical examination [B]						
Oral temperature recorded						
Pre-vaccination serology sample obtained [C]						
Review of inclusion/exclusion criteria						
Administration of study vaccine						
Diary card [D] completed by participants (Day 0-3)						
Diary card mailed to study site						
Diary card review and AE assessment				[E]		
Post-vaccination serology sample obtained [C]						
Collection of SAEs (Day 1-21)						
Review of concomitant medication						
Nasal swab for intercurrent flu-like illness *						[F]

A Including: concomitant medication, previous vaccinations and previous influenza illness
B If clinically indicated
C HAI and SRH assays (B Strain only) influenza vaccine status, AEs to previous
D 4-Day Solicited and Unsolicited AE diary card
E Adverse events assessment only
F Occurrence of flu-like illness only
* If applicable

Source: Protocol, Appendix 1 (Appendix 16.1.1)

• Subjects received a pre-vaccination history, targeted physical if indicated, and completed a 4-day post-vaccination diary card for solicited and unsolicited AEs. Subjects who had not returned their diary cards by Day 9 were contacted by telephone.

• All AEs of more than 2 days duration and all SAEs for the duration of the study were recorded in the subject's CRF.

• At Exit Visit Day 21 ± 4, subjects were re-evaluated for AEs and, if indicated, with a medical evaluation.

• Intercurrent flu-like illness (ILI) was defined as oral temperature > 37.5ºC and at least one flu-like symptom: sore throat, cough, myalgia, chills, rigors, headache, or malaise. Subjects experiencing an ILI between Days 0 and Day 21 ± 4 were evaluated at the investigative site.

• The intensity/severity of Unsolicited AEs were graded as follows:

Mild: Symptoms were easily tolerated and there was no interference with daily activities.

Moderate: Discomfort enough to cause some interference with daily activities.

Severe: Incapacitating with inability to do work or do usual activity.

• An SAE was defined as an 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 congenital anomaly/birth defect.
- Was a Medically Significant Event: An event that was judged by the treating physician to potentially jeopardize the participant or required medication intervention to prevent one of the outcomes defined as an SAE.

• Any deaths were to be reported to the Chiltern Pharmacovigilance Officer and to the Sponsor Contact at CSL within 24 hours irrespective of cause. The Pharmacovigilance Officer was to provide a report to CSL, the Independent Ethics Committee (IEC), and the Medical and Healthcare Products Regulatory Agency.

• All SAEs were to be reported to the Chiltern Pharmacovigilance Officer within 24 hours. CSL was to be notified within 24 hours and the IEC within a specified time frame. If the SAE was vaccine-related or unexpected, the relevant Competant Authority was notified as well.

• All SAEs were to be followed until resolution or until the subject's condition stabilized.

• Relationship to the study vaccine was categorized as:

- Not related: In the PI/delegate's opinion, there was not a causal relationship

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

8.1.5.1.7 Statistical considerations

• Populations analyzed
- o Safety Population: all participants who received Influenza Vaccine (CSL Limited). This population was used for the Safety Analysis.
- o Evaluable Population: all participants who were vaccinated with Influenza Vaccine (CSL Limited) on Day 0, provided both pre- and post vaccination blood samples, and did not meet any other elimination criteria or have a laboratory-confirmed flu-like illness. This population was used for the Immunogenicity Analysis.

• Descriptive statistics were to be used to present all safety and immunogenicity results.
• Baseline demographics were to be summarized and were based on the Evaluable Population.
• Serum pre- and post-vaccination anti-HI antibody titers for each participant were performed simultaneously and in duplicate on two separate days. The titer was expressed as the geometric mean of the two independent determinations.
• AEs and SAEs were categorized according to the MedDRA preferred term and system organ class.
• The most frequent MedDRA preferred terms (≥ 5% events overall) and system organ class were to be presented.
• No interim analyses were planned.
• Any HI result < 10 (=undetectable) was expressed as 5.
• Sample size was based on CPMP requirements that there be a minimum of 50 participants in each age cohort.

• **Changes in the Statistical Planned Analysis from the Protocol** were reflected in the single Protocol Amendment dated May 26, 2005.
- o Participants with laboratory confirmed ILI were excluded from the Evaluable Population.
- o The definition of Safety Population was broadened to include all participants who received the study vaccine.

• **Changes in the Statistical Planned Analysis after Database Lock**
- o The Adult (n=60) and Older Adult (n=60) Safety population (n=120) was used for

the GMT fold increase (HI titer) analysis for all three vaccine strains.

- **Changes to the conduct of the Study**
  - Post-text Tables 7.1 and 7.2 read "Induration larger than 50mm for 3 days," but data were collected on a daily basis, and the tables should read "Induration greater than 50mm for each Day 0 through 3 post-vaccination.

8.1.5.2 Results of Study CSLCT-NHF-04-99

8.1.5.2.1 Populations enrolled and analyzed

The following table is based on the applicant's Table 2, p 45, Module 5, Volume 24:

Table 8.1.5-2 Participant Disposition Study CSLCT-NHF-04-99

	Adult n (%)	Older Adult n (%)	Total n (%)
Total enrolled	60	60	120
Total vaccinated	60 (100.0)	60 (100.0)	120 (100.0)
Safety population	60 (100.0)	60 (100.0)	120 (100.0)
Evaluable population	60 (100.0)	59 (98.3)	119 (99.2)
Protocol completed	60 (100.0)	60 (100.0)	120 (100.0)
Protocol withdrawals	0	0	0
Reason for withdrawal			
SAE	0	0	0
AE	0	0	0
Protocol violation	0	0	0
Withdrew consent	0	0	0
Lost to follow-up	0	0	0
Death	0	0	0
Other			

Protocol violation	0	1	1
Received prohibited medication	0	1	1

Reviewer comment: All enrolled subjects completed the protocol. Only one subject was

excluded from the Evaluable population for a protocol violation: Participant 9094, an Older Adult, received the pneumococcal vaccine during the study. No participant was withdrawn because of death, SAE, or other AEs. The applicant's data was confirmed by review of the datasets.

Table 8.1.5-3 Demographic Data and Other Baseline Characteristics Study CSLCT-NHF-04-99

Characteristic	Adult (n=60)	Older Adult (n=59)	Total (n=119)
Age (years)			
n	60	59	119
mean (SD)	45.99 (9.549)	66.97 (4.833)	56.39 (12.963)
Gender n, (%)			
Male	14 (23.3)	28 (47.5)	42 (35.3)
Female	46 (76.7)	31 (52.5)	77 (64.7)
Previous influenza vaccination	10 (16.7)	31 (51.7)	41 (34.2)
2001	12 (20.0)	38 (63.3)	50 (41.7)
2002	16 (26.7)	39 (65.0)	55 (45.8)
2003	19 (31.7)	48 (80.0)	67 (55.8)
2004			
Previous influenza illness			
Yes	30 (50.0)	28 (46.7)	58 (48.3)
No	30 (50.0)	32 (53.3)	62 (51.7)

Note: demographic data for age and gender is based on the Evaluable population while history of previous influenza vaccination and illness is based on the Safety population. The tables were combined because the populations are almost identical.

Reviewer comment: The mean age in the Adult group was 45.99 and in the Older Adults 66.97. Male to female ratio was approximately equal in the Older Adult group, but there significantly more females in the Adult group, 76.7%. More Older Adults than Adults had a history of previous influenza vaccination in the four years prior to the study: 51.7-80.0% versus 16.7-31.7%. Approximately half of subjects in both age groups had a history of prior influenza illness.

The applicant's demographic data for gender was confirmed by evaluation of the electronic datasets. However, mean age was not confirmed but the applicant's report appears to be acceptable. The data on previous influenza diagnosis or previous influenza vaccination were not included in the electronic datasets and the applicant's summary review could not be confirmed from an electronic source data.

8.1.5.2.2 Efficacy endpoints for CSLCT-NHF-04-99

• The applicant provided the immunologic endpoints, point estimates with 95% CIs summarized in the table below. The table is based on Tables 4.4, 4.5, and 4.6 Module 5 volume 24.

• Bold italics indicate failure to meet CPMP criteria for immune response.

Table 8.1.5-4 Immunologic endpoints Study CSLCT-NHF-04-99

Strain	Adults ≥18 to <60 (n=60) % 95% CI	Older Adults ≥ 60 (n=59) % 95% CI
H1N1	 EU	 EU
% 4-fold increase in HI titer*	55.0 >40% 42.0, 68.0	***13.6*** >30% **6.0**, 25.0
GMT fold increase	6.18, (4.579) >2.5 4.169, 9.150	2.01 (2.382) >2.0 1.604, 2.522
% with post-vaccination HI antibody titer ≥ 1:40	83.3 >70% 71.0, 92.0	***54.2*** >60% **41.0**, 67.0
H3N2		
% 4-fold increase in HI titer	90.0 >40% 79.0, 96.0	86.4 >30% 75.0, 94.0
GMT fold increase	27.08 (4.198) >2.5 18.692, 39.225	11.72 (3.713) >2.0 8.329, 16.501
% with post-vaccination HI antibody titer ≥ 1:40	98.3 >70% 91.0, 100.0	93.2 >60% 84.0, 98.0
B strain		
% 4-fold increase in HI titer	56.7 >40% 43.0, 69.0	***15.3*** >30% **7.0,** 27.0
GMT fold increase	6.81 (4.251) >2.5 4.683, 9.891	2.07 (2.591) >2.0 1.618, 2.658
% with post-vaccination HI antibody titer ≥ 1:40	***58.3*** >70% **45.0**, 71.0	***42.4*** >60% **30.0**, 56.0

*% 4-fold increase in HI titer = proportion with a four-fold increase in anti-HI antibody titer with a post-vaccination HI antibody titer of at least 1:40.

Reviewer comment: CSL IVV failed to meet CPMP point estimate criteria for proportion with

four-fold increase in HI antibody titer criteria for immune response for H1N1 and B strains in the Older Adult cohort. The vaccine also failed to meet CPMP criteria for proportion with post-vaccination anti-HI antibody titers ≥ 1:40 for B strain in Adults 18 to < 60 and for H1N1 and B strains in Older Adults ≥ 60 years of age. However, because only one of the three criteria needs to be met as a point estimate for each strain in order to receive an overall pass, the study vaccine was judged to meet criteria for immune response in both cohorts by EMEA CPMP criteria.

If FDA criteria are applied to these subjects, only the H3N2 would have fulfilled both immune response criteria for proportion with four-fold increase in HI antibody titer and for proportion with HI titer ≥ 1:40 in both age groups.

8.1.5.2.3 Safety outcomes for CSLCT-NHF-04-99

- There were no deaths, SAEs, severe unsolicited AEs, or discontinuations due to AEs in this study.
- Solicited local and general reactogenicity events are presented in the table below and are derived from the applicant's Tables 6.1, 6.2, 7.1, and 7.2, Module 5, vol 24.
- Reviewer's results from the datasets are identical to the applicant's except where indicated by bold print.

Table 8.1.5-5 Solicited local and general reactogenicity events CSLCT-NHF-04-99

Solicited general and local reactogenicity events	Adult (n=60) %	Older Adult (n=60) %
Fever >38ºC > 24 hr	1.7	1.7
Chills	3.3	3.3
Malaise	18.0	3.3
Induration >50mm on a daily basis	1.7	1.7
Erythema	23.3	10.0
Ecchymosis	5.0	5.0
Pain	45.0	16.7

Percentages are based on the number of subjects in each group experiencing a particular AE.

Note: in this study induration was counted as an AE even if only 1 or 2 days in duration, unlike CSLCT-NHF-05-13 which included only induration > 50mm >3days duration as AEs.

Reviewer comment: Malaise, erythema and pain were the most frequent solicited AEs, and occurred primarily among the Adult cohort. Evaluation of the electronic datasets confirmed the applicant's numbers.

- **Unsolicited Adverse Events**

The applicant's report of unsolicited AEs is summarized in the tables below:

Table 8.1.5-6 Unsolicited AEs by system organ class and preferred term

System organ class/ Preferred term	Adult (n=60) %	Older Adult (n=60) %
%subjects/total# of AEs	13.3	13.3
Infections and infestations	1.7	10.0
URI	1.7	3.3
Herpes zoster	0	1.7
LRI	0	1.7
Otitis externa candida	0	1.7
Tooth abscess	0	1.7
General disorders and admini-stration site conditions	5.0	1.7
Fatigue	1.7	0
Injection site pruritis	0	1.7
Pain	1.7	0
Tenderness	1.7	0
Nervous system disorders	3.3	0
Headache	3.3	0
Cardiac disorders	0	1.7
Arrhythmia	0	1.7
Ear and labyrinth disorders	1.7	0
Ear pain	1.7	0
Eye disorders	1.7	0
Eye swelling	1.7	0
Injury,poisoning,and procedural Complications	0	1.7
Arthropod bite	0	1.7
Musculoskeletal and connective Tissue disorders	1.7	0
arthralgia	1.7	0
Skin and subcutaneous tissue Disorders	1.7	0
rash	1.7	0
Surgical and medical procedures	1.7	0
Nail operation	1.7	0

URI=upper respiratory tract infection
LRI=lower respiratory tract infection
Percentages refer to the number of subjects experiencing an adverse event

Reviewer comment: the overall frequency of unsolicited AEs was very low, the most frequent being upper respiratory infection, headache, and injection site-related conditions. This is similar to adverse events noted among other trivalent inactivated influenza vaccines.

The applicant's data was confirmed by evaluation the electronic source datasets. The numbers of subjects experiencing each AE as expressed by preferred term were identical. The severity of AEs experienced by subjects was also found to be identical, and is summarized in the table below:

Table 8.1.5-7 Medical Officer review of Unsolicited AEs by severity:

	Adult (n=60)	Older Adult (n=60)	Total (n=120)
Total AEs	11	9	20
Mild	2	5	7
Moderate	4	9	13
Severe	0	0	0

Reviewer comment: the review of unsolicited AEs by severity corresponds to the number of events reported by the applicant. The total numbers of subjects experiencing these events were 8 Adults and 8 older adults, for a total of 16. Two subjects experienced two different types of AEs and one experienced 3 different types of AEs. Therefore, number of subjects with AE=16 and total # of AEs = 20.

• **Influenza-like Illness (ILI)**

There was only one subject who had symptoms that met criteria for an ILI. Participant 9104, an Older Adult, did not return for the ILI evaluation visit and, therefore, did not have a nasal swab taken for attempt at viral isolation.

8.1.5.3 Comments and Conclusions Study CSLCT-NHF-04-99

• This study was not designed with a regulatory intent to support U.S. licensure of CSL IVV. The purpose of the study was to evaluate the immunogenicity and safety of the 2005/2006 formulation of CSL's trivalent influenza vaccine in order to maintain licensure in the European Union.

• One of the three immune response criteria must be satisfied for each strain in order for consideration of the vaccine, the vaccine to meet CPMP criteria for yearly licensure by EMEA. The CPMP criteria were met in both cohorts. However, CSL IVV did not meet some of the point estimates for individual strains as noted in the tables above.

• If the FDA criteria were to be applied to these results, only the H3N2 strain would have fulfilled immune response criteria.

• As in the other non-IND studies submitted to the BLA, interpretation of the immunogenicity data is limited by the small sample size and by the uncertain impact of the deep subcutaneous route of administration used to vaccinate all subjects. In addition, the performance of the unvalidated HI assays at a laboratory different from that used in studies CSLCT-FLU-05-09 and CSLCT-NHF-05-15 makes direct comparison of the immunogenicity results less reliable than if the assays had been performed at the same laboratory.

• Regarding local and general reactogenicity events, subjects experienced significant pain, erythema, and malaise, particularly in the Adult group. This may have been related to the deep subcutaneous route of administration. Intensity/severity was not assessed. Unsolicited AEs were very infrequent and none were reported as severe.

• Overall, the safety data collected in this study appears to be similar to the findings in the pivotal study CSL-NHF-05-09 in both young and older healthy adults. Therefore, the safety data may provide support for administration of the vaccine to elderly adults.

• There were no study visits for "intercurrent influenza-like illness", although one study subject was reported to have influenza-like illness.

8.1.6 Trial # 6

8.1.6.1 **Applicant's Protocol Number** CSLCT-NHF-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)."

8.1.6.1.1 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:
  - o Local and systemic solicited AEs for 7 days post each vaccination;
  - o Unsolicited Adverse Events for 30 days post each vaccination;
  - o Serious Adverse Events 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.*

8.1.6.1.2 **Design Overview**

• This was a Phase III, open-label, non-randomized, unblinded 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).
• Day 0, Vaccination Dose 1, Visit 1: medical evaluation, 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.

8.1.6.1.3 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.

8.1.6.1.4 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)
- 15 µg 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: 090600101.

8.1.6.1.5 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%.

8.1.6.1.6 Surveillance/Monitoring

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

Table 8.1.6-1 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-like Illness (including throat swabs if applicable)		Participants may have attended additional visits for medical confirmation of flu-like 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.
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

* 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.

• All deaths were reported immediately to the CSL Clinical Research Department and the Independent Ethics Committee and IRB.

• 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.

8.1.6.1.7 Statistical Considerations and Planned Analyses

• Sample size was based on standards set by the Swedish Medical Products Agency specific to safety studies of influenza vaccine in pediatric populations

• 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 titre <10 pre-vaccination.
- Geometric mean of pre-vaccination serum HI titres and 95% confidence interval.
- Pre-vaccination seroprotection rate: Number and percentage of evaluable participants with pre-vaccination serum HI titres ≥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 titres and 95% confidence interval.
- Seroconversion rate: Number and percentage of evaluable participants with serum HI titre <10 pre-vaccination (undetectable) and an increase in serum HI titre to ≥40 post-vaccination.
- Significant increase: Number and percentage of evaluable participants with serum HI titre ≥10 pre-vaccination and at least a four-fold antibody titre 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 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.
- A table presenting the concomitant medications started after the baseline Day 0 visit was generated after the database lock.

8.1.6.2 Results of Study CSLCT-FLU-04-05

8.1.6.2.1 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 8.1.6-2 Participant Disposition Study CSLCT-FLU-04-05

	Group A ≥6mos to <3yrs n (%)	Group B ≥3yrs to <9yrs n (%)	Total 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 Received Dose 1 + 2	 143 139	 144 132	 287 271
Protocol completed	148	145	293 (98.3)
Protocol withdrawals	3 (2.0)	2	5 (1.7)

		(1.4)	
Reason for withdrawal SAE AE Protocol violation Withdrew consent Moved away Lost to follow-up Other	 0 0 2 (1.3) 0 1 (0.7) 0	 0 0 2 (1.4) 0 0 0	 0 0 4 (1.3) 0 1 (0.3) 0
Protocol violation	0	0	0

Reviewer comment: Of the 298 participants enrolled, 293 completed the study. Four withdrew consent and one was lost to follow-up. There were 17 protocol deviations related to vaccine administration and 101 protocol deviations related to procedural deviations, but no subject was withdrawn from the study because of a protocol deviation.
No protocol violations were reported by the applicant.

Table 8.1.6-3 Demographics and Other Baseline Characteristics CSLCT-FLU-04-05
(based on applicant's Table III Module 5 Vol 26 p43)

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)
Gender Male Female	 74 (49.0) 77 (51.0)	 66 (44.9) 81 (55.1)
Prior influenza illness Yes No	 19 (12.6) 132 (87.4)	 15 (10.2) 132(89.8)
Prior Influenza Vaccination Yes No	 0 151 (100)	 0 147 (100)

8.1.6.2.2 Efficacy endpoints for CSLCT-FLU-04-05

Reviewer comment: FDA did not specifically request immunogenicity data from this pediatric study for formal review in support of the BLA. However, immunogenicity data was included by the applicant in the CSR and is summarized in the table below which is based on the applicant's Tables IV and V pp46-47 Module 5 Vol 26 Section 5.3.5.2-3:

Table 8.1.6-4 Point estimates of immune response Study CSLCT-FLU-04-05

Strain/ criterion	CPMP criteria		FDA criteria	Group A ≥6mos to <3yrs		Group B ≥3yrs to <9yrs	
	Point estimate	Lower bound 95%	Dose 1 n=143	Dose 2 n=139		Dose1 n=144	Dose 2 n=132

		CI				
H1N1 % 4-fold increase * Fold increase GMT % with HI ≥ 1:40**	>40% >2.5 >70%	>40% n/a >70%	16.1% 3.1 16.1%	95.0% 25.6 95.7%	24.3% 3.4 25.7%	93.9% 22.3 95.5%
H3N2 %4-fold increase Fold increase GMT % with HI ≥1:40	>40% >2.5 >70%	>40% n/a >70%	86.0% 13.7 97.9%	90.6% 49.6 100%	68.1% 6.1 98.6%	70.5 8.8 100%
B Strain % 4-fold increase Fold increase GMT % with HI ≥ 1:40	>40% >2.5 >70%	>40% n/a >70%	20.3% 3.5 21.0%	94.2% 22.3 95.7%	32.6% 4.3 34.0%	93.2% 22.2 94.7%

*% 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.

Reviewer comment: Following the first dose of vaccine, both age groups met the three immunogenicity endpoints for strain H3N2, but as expected in an "unprimed" pediatric population, did not meet the four-fold increase or the proportion with HI titer ≥ 1:40 criteria for strains H1N1 and strain B. However, both groups of children met all three CPMP point estimate immunogenicity endpoints after 2 doses of vaccine. The lower bound of the 95% confidence interval for the % four-fold increase and the % with HI titer ≥1:40 were above 40% and 70%, respectively, for each of the three vaccine strains.

Electronic datasets were not submitted for this study. The reviewer therefore evaluated the applicant's line listings as source data for the immunogenicity results. Line listings 16.2.8.1, 16.2.8.2, and 16.2.8.3 (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 analysis:

Table 8.1.6-5 Number of Subjects with either a 4-Fold Increase in HI Titer (minimum 1:40) or with a Post Vaccination HI Titer of ≥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 % HI ≥1:40	 127 (93.4%) 128 (94.1%)	 121 (93.1%) 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.

Reviewer comment: there were small differences in the applicant and reviewer numbers of evaluable subjects, but the overall immune response rates were similar to the applicant's results. Both groups of children met all three immunogenicity endpoints after two doses of vaccine.

8.1.6.2.3 Safety outcomes for study CSLCT-FLU-04-05

• Safety data was summarized by the applicant in tabular form. There were no electronic datasets provided for this study from which to confirm the applicant's reports.

• 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.

• Solicited local and systemic AEs are summarized in the table below, based on the applicant's Table 14.4.1.1, Module 5, Vol 26, section 14, p 15.

Table 8.1.6-6 Solicited local and systemic AEs 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 (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)
Local AEs						
Pain	29.8	5.3	1.3	46.3	10.9	2.0
Redness	26.5	8.6	0.7	26.5	9.5	0.7
Swelling	10.6	4.6	0.7	16.3	6.8	1.4
Systemic AEs						
Fever	19.9	2.6	0	11.6	2.7	1.4
Headache	2.0	0	0	8.2	3.4	2.0
Cough	19.9	1.3	0	15.0	3.4	0.7
Sore throat	1.4	0.7	0	6.8	0.7	0.7
Rhinitis	35.8	1.3	0	19.7	1.4	0
Wheezing	2.6	0.7	0	2.7	0	0
Myalgia	0.7	0	0	9.5	2.7	1.4
Ear ache	2.7	0.7	0	4.1	0	0
Vomiting/ Diarrhea	12.6	1.3	0.7	3.4	2.0	0.7

Loss of Appetite	15.2	3.3	0.7	4.8	2.0	0.7
Irritability	32.5	13.9	1.3	13.6	6.1	0.7

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

Reviewer Comment: According to the sponsor's data, pain, headache, sore throat, myalgia and ear ache may not have been assessed in all participants (one or two) inGroup A, resulting in slightly different denominators and percentages.

Table 8.1.6-7 Solicited local and systemic AEs 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 %	Grade 1 %	Grade 2 %	Grade 3 %
Local AEs						
Pain	25.2	11.9	0	42.2	17.7	2.0
Redness	31.1	6.6	0	26.5	12.2	6.8
Swelling	17.2	3.3	0	17.0	8.2	2.0
Systemic AEs						
Fever	15.2	6.6	0.7	7.5	0.7	0
Headache	2.0	0.7	0.7	8.8	1.4	0.7
Cough	23.8	6.6	1.3	17.7	1.4	0.7
Sore throat	2.7	1.3	1.3	8.2	2.0	0.7
Rhinitis	37.1	9.3	1.3	25.9	2.7	0
Wheezing	6.6	2.0	0	1.4	0.7	0
Myalgia	2.0	0.7	0	6.1	2.0	0
Ear ache	2.0	1.3	0	0.7	0.7	0
Vomiting/ Diarrhea	9.3	2.0	2.6	6.1	0.7	0
Loss of Appetite	15.9	5.3	2.6	4.8	0.7	0
Irritability	24.5	11.9	4.6	15.0	2.0	0

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

Reviewer comment: For the younger age Group A, the overall frequency of local and systemic solicited AEs after Dose 1 compared to Dose 2 were similar. Pain, redness, rhinitis, irritability, cough, and fever were the most frequent events. These were primarily mild to moderate. There were very few severe reactions, and for events where parents did not report severity, a grade three was assigned. The majority of events were considered vaccine-related by the sponsor.

For the older age Group B, there were relatively fewer systemic reactions and more local reactions, again mostly mild to moderate in severity. Pain, redness, rhinitis, irritability, and cough were most frequent. The majority of events were considered vaccine-related.

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 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.

- **Unsolicited AEs**

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 26, section 14, p 17:

Table 8.1.6-8 Total number of Unsolicited AEs collected within 30 days of receiving Dose 1 or Dose 2, intensity and causality

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)

Reviewer comment: The majority of events were considered non-serious and unrelated to the Study Vaccine. Three SAEs reported within the 30-day period following Dose 1 or Dose 2, were: diarrhea with dehydration and fall; viral pneumonia; and Respiratory Syncitial Virus Bronchiolitis. None of these were considered vaccine-related. Two other unrelated SAEs were reported beyond the 30-day post-vaccination period. The CRFs for the SAEs were requested from the applicant and are reviewed below.

The following table is based on the applicant's Table 14.4.4.1, Mod 5, Vol 26, Sect 14, p 21. The Reviewer has selected those AEs in each age group which occurred with a frequency of ≥ 5%:

Table 8.1.6-9 Unsolicited AEs Occurring with a Frequency of ≥ 5% within thirty 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
Vomiting	6.4	7.9	4.8
General disorders/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

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

Reviewer comment: 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. Of these, 76 (11.6%) were judged possibly, probably or definitely related to the Study Vaccine. Of the total number of AEs, 76 (11.6%) were graded as severe. There were no serious AEs which were reported as vaccine-related, and no withdrawals from the study due to unsolicited AEs. There were no deaths.

The most frequent unsolicited AEs in the younger age Group A were teething, influenza-like illness, rhinitis, URI, and cough. The most frequent AEs by preferred term in the older age Group B were rhinitis, cough, ILI, nasopharyngitis, and rhinorrhea.

- The following table is based on the Reviewer's evaluation of the applicant's Line Listings of Unsolicited AE's. The number of subjects with moderate or severe unsolicited AE's and relationship to the study vaccine are compared to the applicant's summary data (Table 14.4.2.1, Module 5, Volume 26, Section 14, p17.)

Table 8.1.6-10 Unsolicited AE's by Severity and Causality,

Derived from Line Listings, Study CSLCT-FLU-04-05

Subjects with AE/ Relatedness	Group A ≥6 mos to <3 years		Group B ≥3 years to <9 years	
	reviewer	applicant	reviewer	applicant
Moderate AE	155	175	98	98
Related mod	9	*	7	*
Severe AE	41	41	34	35
Related severe	5	*	6	*

*applicant did not provide summary data of related AE's according to severity grade

Non-vaccine-related included unrelated or unlikely Overall, no significant differences were found between thimerosal-containing versus thimerosal-free vaccine in either the Adult or Older Adult populations.

Reviewer comment: there is a large discrepancy between the reviewer and applicant's number

of subjects who reported moderate AE's. We will take the conservative approach and assume that the applicant's numbers are correct. If the safety results of this study were to be summarized in a regulatory document or in product labeling, the applicant's number of adverse events would be further clarified.

10.4.5 Potential Product-Product Interactions

Table 8.1.6-11 All Vaccine-Related Severe Unsolicited AEs • Potentiation of warfarin effect by influenza vaccine has been suggested, but the literature to support this is contradictory and the post-marketing data has not been sufficient to suggest causality. The applicant reports no significant signals regarding aberrant INRs have emerged from post-marketing data.

Derived from line listings, Study CSLCT-FLU-04-05

Group Subject **10.4.9 Pregancy and Lactation**	Severe AE	Relationship
CSL has not actively recruited pregnant or lactating females in any of their studies. The post-marketing experience in pregnant females is noted below.		

Group A The following summaries are provided by the applicant in the BLA: 01/126/A• Use in children	ILI o Thimerosal-free IVV: a total of 27 AEs, 7 serious, in children 10 months to 17 years. Majority were flu-like symptoms. There were isolated cases of idiopathic thrombocytopenia, GBS, and transverse myelitis. Pyrexia (5/12/05)o Thimerosal-containing IVV: a total of 9 reports, 8 serious. Flu-like symptoms, hypersensitivity, and 3 cases of poorly documented seizures and Bell's palsy which were considered not likely to be vaccine-related. Pyrexia (5/14/05)• Pregnancy and Lactation	Definitely o As of August 31, 2006, a total of three cases of maternal exposure, all with thimerosal-free vaccine during the first trimester of pregnancy have been reported. Of these, one abnormal outcome of spontaneous abortion at week 13 was reported. The subject, whose age is unknown, received IVV at week 7. No other details were available according to the applicant. The outcomes of the other two pregnancies are unknown according to the applicant. Definitely definitely o There are no other reports of paternal or neonatal exposure through lactation.

01/127/A• The applicant reports having compiled a total of 7 post-marketing reports for various global regulatory agencies since 1985. The majority of spontaneously reported AEs have been influenza-like symptoms and injection site reactions.	Irritability	Definitely • The applicant has included a narrative of cumulative post-marketing data for transverse myelitis, GBS, and immune system disorders:
01/151/Ao Transverse myelitis: 9 spontaneous reports, insufficient diagnostic evidence, no direct causal evidence.	ILI	Definitely o Guillain Barre Syndrome: 25 cumulative spontaneous reports for thimerosal and thimerosal-free product, one fatal case according to the post-marketing experience narrative, Module 5, Volume 29, Section 5.3.6-8, pp 34-35. Case information is limited according to the applicant, and confounded by viral illnesses or co-suspect vaccines. Applicant concludes that no significant safety issue is raised in view of the extensive use of the CSL IVV and the background rate for GBS of 10-20 cases per million per year.

Group B Reviewer comment: there appear to be not one, but two fatal cases of GBS cited in the BLA. One is mentioned in the Post-marketing experience Module 5 Volume 29 Section 5.3.6-8, p34-35. A 68 year old male who developed GBS 3 weeks after influenza vaccination, complicated by respiratory failure and death despite ventilatory support and 5 days of IVIG. No post-mortem details were available to the applicant. The second fatal case of suspected GBS was reported as Amendment 26 to BB-IND ---------- and is described in Section 10.3.2 above. 01/057/B	ILI	Definitely
01/085/B	ILI	Probably
01/088/B	Abdominal pain	Definitely
01/095/B	Pyrexia Vomiting	Probably Probably
01/126/B	Fatigue	Definitely

*ILI = influenza-like illness

Reviewer Comment: of 76 reported severe unsolicited AEs, 11 events in 8 subjects (10.5%) were judged related to the study vaccine. These reactions were primarily pyrexia and ILI.

- **SAE Case Report Forms**

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 BLA. The following SAE CRFs were reviewed:

- 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. Resolved by May 23, 2007.

- Subject B087: 3 year old female vaccinated April 5, 2005. Severe ILI, onset Day 5 post-vaccination, diagnosed as viral pneumonia. Judged not vaccine-related. Resolved June 2, 2005.Throat swab collected.
- Subject A013: 13 month old female vaccinated April 22, 2005. Hospitalized ---------- 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. Hospitalized ---------- with E.coli UTI, reflux, 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. Hospitalized ---------- with new onset Type I diabetes mellitus. Discharged ----------. Judged not vaccine-related.

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

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

• This study was not designed with a regulatory intent to support U.S. licensure of CSL's Inactivated Influenza Vaccine. The purpose of the study was to evaluate the safety and immunogenicity of the 2005/2006 formulation in support of European licensure for a pediatric indication.
• 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. The frequency of vaccine-related Unsolicited AEs was reported as at most 11.6% with no serious vaccine-related events.
• The safety data submitted in this study appears to support the BLA in a general sense, and may be supportive of data which will be submitted in a future post-licensure study in the pediatric population.
• The secondary endpoints of immunogenicity were not specifically requested by FDA for formal review in support of this BLA. However, summary data presented by the applicant suggests that the vaccine satisfies the surrogate immunogenicity endpoints after 2 doses in the pediatric populations studied. A post-marketing study in the pediatric population will be undertaken to support a pediatric indication.
• The study provided safety data at timepoints greater than 21 days post-vaccination. There were no new safety concerns identified in this study.

8.1.7 Integrated Safety Summaries for Subjects ≥65 Years of Age

• The applicant provided two integrated summaries of safety data in subjects ≥65 years of age:

- One from the four supporting non-IND studies submitted to the BLA (CSLCT-NHF-05-15, CSLCT-NHF-05-11, CSLCT-NHF-05-13, and CSLCT-NHF-04-99), and

o One from the 23 older studies conducted in Australia to support licensure and registration.

8.1.7.1 Integrated Summary of Safety Data in the ≥ 65 year old population from the Non-IND Studies submitted to the BLA.

8.1.7.1.1 Solicited Adverse Events.

The table below is reproduced from the applicant's table in Module 2 Volume 2 Section 2.7.4, p 179. In response to FDA quiries, CSL provided corrections to some miscalculations in the original BLA submission on June 13, 2007 in Amendment 125254/0.4.

Table 8.1.7-1 Integrated Post-hoc Analysis of Solicited AEs in subjects ≥65 years of age, non-IND studies submitted to the BLA

Solicited Adverse Event	Totals, all 4 studies (integrated)		
	CSL IVV n=343 %	Influsplit n=69 %	Mutagrip n=60 %
Local			
Induration >50mm	0.6	ND	1.7
Induration>50mm x 3 days	0.0	ND	0
Ecchymosis	5.2	1.4	6.7
Erythema	18.1	8.7	11.7
Pain	9.9	0	3.3
Systemic			
Malaise	7.2	7.2	3.3
Fever>38°C≥24hr	1.4	1.4	1.7
Chills	5.8	5.8	1.7

Note: all CSL vaccine used in these studies were thimerosal-free.
ND = not done

• Reviewer comment: The most frequent solicited AEs for CSL IVV recipients in the age group ≥ 65 years were erythema, pain,malaise, chills, and ecchymosis. Erythema and pain at the injection site appeared more frequent with CSL IVV than with comparator recipients. Compared to adults aged ≥ 18 to < 65 in the pivotal study CSLCT-NHF-05-09, there was less induration, pain and malaise, and generally similar rates of ecchymosis, erythema, fever, and chills among elderly subjects. Solicited AEs in this age group do not appear unexpected and seem acceptable.

8.1.7.1.2 Unsolicited Adverse Events

• The sponsor did not provide post-hoc integrated data for unsolicited adverse events in the non-IND studies for the population ≥ 65 with the original BLA submission, but at FDA's request, supplied this information in Amendment 125254/0.4 dated June 13, 2007. The following data is based on that information:

Table 8.1.7-2 Integrated Post-hoc Analysis of Unsolicited AEs occurring in ≥3% of subjects ≥65 years of age from non-IND studies submitted to the BLA

System Organ Class Preferred Term	Totals, all 4 studies (integrated)		
	CSL IVV n=343 %	Influsplit n=69 %	Mutagrip n=60 %
Respiratory, thoracic, &mediastinal disorders	**9.0**	**10.1**	**0.0**
Nasal congestion	4.1	2.9	0.0
Rhinorrhea	3.2	5.8	0.0
Nervous system disorders	**6.1**	**8.7**	**1.7**
Headache	5.5	7.2	1.7
Gastrointestinal disorders	**2.9**	**4.3**	**0.0**
Musculoskeletal and connective tissue disorders *	**3.2**	**1.4**	**1.7**
Infections and infestations	**2.9**	**1.4**	**0.0**
General disorders and administration site conditions	**1.5**	**2.9**	**0.0**
Eye disorders	**0.9**	**0.0**	**0.0**
Skin and subcutaneous tissue disorders	**0.3**	**2.9**	**0.0**
Injury, poisoning and procedural complications	**0.9**	**1.4**	**0.0**
Ear and labyrinth disorders	**0.9**	**0.0**	**0.0**
Surgical and medical procedures	**0.3**	**0.0**	**0.0**
Investigations	**0.3**	**0.0**	**0.0**
Renal and urinary disorders	**0.3**	**0.0**	**0.0**
Vascular disorders	**0.3**	**0.0**	**0.0**
Psychiatric disorders	**0.0**	**1.4**	**0.0**

Reproductive system and breast disorders	**0.0**	**1.4**	**0.0**
Immune system disorders	**0.0**	**1.4**	**0.0**
Cardiac disorders			

% based on number of subjects in the respective groups
* for some System Organ Classes, there were no AEs/preferred terms which occurred in ≥3% of subjects

Reviewer Comment: Overall, unsolicited AEs in these studies were infrequent. The most commonly reported preferred terms by CSL IVV recipients were headache (5.5%), nasal congestion (4.1%), and rhinorrhea (3.2%). Study CSLCT-NHF-05-15 was disproportionately represented relative to the other non-IND studies in this summary because of the greater number of subjects (206 out of 343, 60%) and because unsolicited AEs were reported for 21 days post-vaccination as opposed to 3 days post-vaccination in the other three studies.

8.1.7.2 Integrated Age-Stratified Safety Data from 23 Older Supportive Studies

- To enhance the safety data presented in CSLCT-FLU-05-15 and in the post hoc analysis of subjects ≥ 65 in studies CSLCT-FLU-05-11, CSLCT-FLU-05-13, and CSLCT-FLU-04-99, the applicant agreed to provide stratified safety data from twenty-three older supportive studies conducted in Australia to support licensure and annual registration.
- The data are presented in the tables below and are based on the applicant's Tables 2.7.4.2.2, 2.7.4.2.3, 2.7.4.2.4, and 2.7.4.2.5, and on the applicant's Amendment 125254/0.4 which corrected errors in calculations submitted with the original BLA:

8.1.7.2.1 Solicited AEs

Table 8.1.7-3 Cumulative Age-Stratified Solicited AEs from 23 Early Supportive Studies

	CSLCT-FLU02-86 Thimerosal-free			Additional early studies Thimerosal-containing CSL influenza vaccine*
	≥60 to <65years n=24 %	≥65 years n=35 %	≥60to<65years n=73 %	≥65years n=245 %
Local reactions				
Induration	8.3	2.9	12.3	13.9
Induration>50mm >3 days	0	0	2.7	1.2
Erythema	8.3	14.3	12.3	14.3

Ecchymosis	4.2	5.7	2.7	4.1
Pain	20.8	25.7	49.3	31.9
Swelling **	n/a	n/a	17.6	12.1
Warmth	n/a	n/a	23.3	20.0
General symptoms				
Fever >38°C	0	0	0	1.2
Feeling hot/warm***	4.2	0	19.6	6.6
Shivering	8.3	2.9	8.2	2.9
Malaise	n/a	n/a	15.1	13.9
Myalgia **	n/a	n/a	21.6	7.1
Sweating	n/a	n/a	1.4	1.6
Headache **	n/a	n/a	25.5	21.7
Nausea **	n/a	n/a	5.9	4.5
Insomnia	n/a	n/a	4.1	8.2

% represents proportion of subjects with a given symptom in respective group
*CSLCT-FLU-00-77, CSLCT-FLU-99-67, CSLCT-98-57, CSLCT-FLU-97-53,CSLCT-FLU-96-48
**total number of subjects reduced, symptom not reported/recorded for CSLCT-FLU-96-48. For ≥ 60 to <65 years, n=51. For ≥ 65 years, n=198.
***total number of subjects reduced, symptom not reported/recorded for CSLCT-FLU-99-67, 97-53, or 96-48. For ≥ 60 to < 65 years, n=30. For ≥ 65 years, n=89.

• For the five studies which used thimerosal-containing vaccine, the applicant also provided a cumulative post hoc analysis comparing the more frequent solicited AEs with the younger population:

Table 8.1.7-4 Solicited AEs among different age groups

Adverse Event	<60 years n=978 %	≥60 to < 65 years n=73 %	≥ 65 years n=245 %
Injection site pain	71.1	50.7	31.0
Headache	36.4	29.4	21.1
Injection site warmth	29.7	23.3	20.0
Myalgia	22.8	23.5	7.6

% based on number of subjects with a given AE in the respective group

• Reviewer comment: The most frequent solicited symptoms in these studies were injection site pain, swelling, warmth, myalgia, and headache. There was no difference in these events in the ≥ 65 year old group compared to the 60 to <65 year olds, and in fact, from the applicant's summary of the more frequent solicited AEs, it appears that the

frequency of these solicited AEs declines with increasing age.

• The applicant did not collect data regarding the severity of these reactions.

8.1.7.2.2 Unsolicited AEs

Table 8.1.7-8 Cumulative Age-Stratified Non-serious Unsolicited AEs from 23 Early Studies

	CSLCT-FLU-02-86 Thimerosal-free		Additional Early Studies Thimerosal-containing CSL influenza vaccine*	
Organ system Preferred term	≥60 to <65years n=24 %	≥65 years n=35 %	≥60 to <65years n=51 %	≥ 65 years n=198 %
Ear/labyrinth Disorders Ear pain	4.2 4.2	0 0	2.0	1.5
Gastrointesinal disorders Abdominal pain Diarrhea	8.3 n/a 8.3	0 n/a 0	5.8 3.9 0	3.0 0 1.5
General and Admini-stration site disorders Fatigue	8.3 8.3	n/a	n/a	n/a
Musculoskeletal/ Connective tissue ds Muscle stiffness Myalgia	8.3 4.2 4.2	0 0 0	5.8 0	2.0 0.5
Nervous system ds Headache	12.5 12.5	11.4 5.7	3.9 3.9	3.5 1.5
Respiratory,thoracic, mediastinal disorders Cough Pharyngolaryngeal pain Upper resp infection	4.6 0 4.2 n/a	25.7 2.9 2.9 n/a	15.7 3.9 n/a 3.9	10.1 0.5 n/a 3.0

*CSLCT-FLU-00-77, CSLCT-FLU-99-67, CSLCT-FLU-98-57, CSLCT-FLU-97-53

Unsolicited AEs were not collected for CSLCT-FLU-96-48 in accordance with the protocol. Preferred terms and System Organ Class are specified where the frequency of the preferred term in any group was ≥ 3.0%.

• Reviewer comment: The overall incidence of unsolicited AEs in the ≥ 65 year old population was low and appeared to be lower than the 60 to < 65 year old age group. The most frequent individual events in the ≥ 65 year old group were headache, cough, pharyngolaryngeal pain, and upper respiratory infection. Of these only headache occurred with a frequency of >5.0%.

8.1.7.2.3 SAEs

• Only 2 SAEs were reported by the applicant as occurring during these 6 early studies. One was severe esophageal spasm and the other a myocardial infarction, neither of which was judged to be vaccine-related.

8.1.7.3 Comments and Conclusions Integrated Safety Data from the non-IND Studies and 23 Older Studies in Persons ≥ 65 years of age:

• Although the post hoc summaries and analyses do not include severity of AEs for the 23 older studies, CSL's safety data appears to indicate that adverse events in the population ≥ 65 years of age do not differ significantly from the younger population.
• Overall the safety data from these studies demonstrate no unusual patterns or unexpected results, and appears to provide supportive safety data.

Overview of Efficacy Across Trials

9.1 Indication

Active immunization of persons 18 years and older against influenza disease caused by influenza virus subtypes A and type B present in the vaccine.

9.1.1 Methods

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 addition to the adult studies, a fifth non-IND study in a pediatric population age 6 months to 9 years of age, 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 this study. The reviewer evaluated source data which consisted of line listings.

9.1.2 Efficacy Endpoints

• The HI assay for studies CSLCT-FLU-05-09 was validated and was performed at ---------- as was the assay for study CSLCT-NHF-05-15. The HI assays for the other non-IND studies were performed by ----------.

9.1.3 Study Design

• Five studies were presented to the BLA in support of efficacy. The pivotal US IND Phase III study CSLCT-FLU-05-09 was placebo-controlled. Of the non-IND studies, CSLCT-NHF-05-15 and CSLCT-NHF-05-11 were comparator-controlled, and CSLCT-NHF-05-13 and CSLCT-NHF-04-99 were uncontrolled trials. CSLCT-NHF-04-99 was a Phase III study, while the remaining non-IND studies were Phase IV studies performed in accordance with annual requirements for licensure in the European Union. CSLCT-FLU-05-09 included only adults ≥ 18 to < 65 years, but randomization was stratified based on age, 18-49 years and 50-64 years, with a minimum number of subjects in the 50-64 age range to be no less than 25%.
• Comparative demographic data across the studies is presented in the table below and is modified from the applicant's Table 2.5.6 Module 2 Volume 1 Section 2.5 p20-22:

Table 9-1 Study Design Efficacy Trials

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 Chiltern Research Center, in Slough, England, just west of London.

Table 9-2 Baseline Characteristics Across Studies

Study Treatment group	Age group	N	Mean age (years)	Male/ Female %	Prior year Flu vaccine

CSLCT-FLU-05-09					
Thimerosal	18to<65	823	38	37/63	48%
Thimerosal-free	18to<65	266	38.2	39/61	45%
CSLCT-NHF-05-15	≥65	206	71.5	50/50	87%
CSLCT-NHF-05-11	18to<60	102	42.4	38/62	18%

CSLCT-NHF-05-13	18to<60 ≥60	60 60	40.7 66.9	35/65 55/45	57% 100%
CSLCT-NHF-04-99	18to<60 ≥60	60 60	46.0 67.0	23/77 48/52	32% 80%

Reviewer comment: Relative to the pivotal study, the mean age of subjects in the non-IND studies was greater and more subjects in the older age groups had received influenza vaccination in the previous year. Overall there were more females than males across the studies.

• The pivotal study CSLCT-FLU-05-09 was performed at multiple sites in the United States. The supporting four non-IND studies were conducted at a single site (Chiltern Research Center, Slough) in the United Kingdom just west of London. Specific race/ethnicity data was not collected for the UK studies, but the applicant indicates that recruitment of subjects was primarily from the local population. Comparative census data derived from the applicant (Module 2 Volume 1 Section 2.5.4.3), the Brookings Institute, and the US Census 2000 are presented in the table below:

Table 9-3 Race/Ethnicity Across Studies

Race/Ethnicity	CSLCT-FLU-05-09	US 2000	Slough	England
Total population	n=1403, (%)	%	n=119,067 %	n=49,138,831 %
White	1103 (78.6)	75.1	63.7	90.9
Mixed		2.4	2.3	1.3
Asian	83 (5.9)	3.6	27.9	4.6
Black	165 (11.8)	12.3	5.1	2.3
Pacific Islander		0.1		
Other		5.5		
Hispanic *	52 (3.7)	12.5		

*Race and Hispanic origin are considered two separate concepts. The US Census Bureau in 2000 considered Hispanic or Latino as persons of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin regardless of race. Persons were first asked whether they considered themselves Hispanic or non-Hispanic, and were then asked what they considered to be their race.

Reviewer comment: Comparing these demographics, there may have been an overrepresentation of Asians in the UK study and an under representation of Blacks and Hispanics relative to the US population.

Reviewer comment: The inclusion and exclusion criteria were very similar across studies as were trial procedures.

• All five studies used the Hemagglutinin Inhibition (HI) Assay to measure serum anti-HI antibody titers as noted above.

• Criteria for Assessment of Immune Response
  - For the pivotal study CSLCT-FLU-05-09, criteria for adults ≥ 18 to < 65 years of age set forth by the previously referenced FDA Draft Guidance for Industry, March 2006, now published in Final version May 2007, were applied. These criteria were prespecified for Study CSLCT-FLU-05-09. For the four supporting non-IND studies, these criteria were also applied to post hoc analyses after stratifying subjects by age ≥ 18 to < 65 years and ≥ 65 years.
  - For the four supporting non-IND studies, CPMP criteria, also previously referenced, were applied to the appropriate age groups: ≥ 18 to < 60 years and ≥ 60 years. In addition, for study CSLCT-NHF-05-15, the primary endpoint required that subjects meet both criteria for seroconversion and proportion with HI titer ≥ 1:40.

• Product equivalence
  - CSL's split virion, inactivated trivalent influenza vaccine (CSL IVV) is marketed under several different trade or proprietary names worldwide including: 'Fluvax', 'CSL IVV', 'Afluria', 'Influenza Vaccine-CSL Limited', and 'CSL Limited Inactivated Influenza Vaccine'. These are considered equivalent drug product and will be referred to as CSL IVV heretofore.
  - Influsplit, the comparator vaccine used in CSLCT-NHF-05-15, is made by GlaxoSmithKline (GSK), is thimerosal-free, and is considered equivalent to US-licensed Fluarix.
  - Mutagrip, the comparator vaccine used in CSLCT-NHF-05-11, is made by Sanofi Pasteur SA, is thimerosal-free, and is licensed in the EU but not in the US.
  - All influenza vaccines used in the efficacy trials were split virion, inactivated, trivalent, propagated in embryonated hen's eggs.
  - Each vaccine used in the efficacy trials used 15µg each of H1N1strain, H3N2 strain, and B strain for a total of 45µg of influenza antigen.

Table 9-4 Vaccine Composition by Year and Clinical Trial

Year	Study	H1N1	H3N2	B strain
2006	05-09	A/New Caledonia/20/99	A/New York/52/2004	B/Malaysia/2506/2004
	05-15	A/New Caledonia/20/99	A/Hiroshima/52/2004	B/Malaysia/2506/2004
	05-13	A/New Caledonia/20/99	A/Hiroshima/52/2004	B/Malaysia/2506/2004

2005	05-11	A/New Caledonia/20/99	A/New York/52/2004	B/Jiangsu/10/2003	
	04-99	A/New Caledonia/20/99	A/New York/52/2004	B/Jiangsu/10/2003	

• Route of administration across studies

Table 9-5 Route of administration (Safety population)

Study	N	SQ n (%)	IM n (%)	Unknown n (%)
CSLCT-FLU-05-09	1089		1089 (100%)	
CSLCT-NHF-05-15 CSL IVV Influsplit	 206 68	 206 (100%) 6 (8.8%)	 0 (0%) 62 (91.2%)	
CSLCT-NHF-05-11	406*	404 (99.5%)	0	2 (0.5%)
CSLCT-NHF-05-13	120	23 (19.1%)	97 (80.8%)	
CSLCT-NHF-04-99	120	120 (100.0%)	0	

*applicant stated that all subjects in both CSL IVV and Mutagrip groups were vaccinated by deep SQ route, except for 2 subjects in whom the route could not be verified.

9.1.4 Efficacy Results Across Studies

The following tables summarize the efficacy data from the five studies submitted to the BLA for Efficacy Review (based on applicant's tables Module 2 Volume 1 Section 2.5 and 2.7.3):

Table 9-6 Summary of Efficacy Results in Adults ≥18 to <60 years of age from Controlled Studies submitted to the BLA*

Study	A/H1N1	A/H3N2	B strain
	%4-FI %≥ 1:40 *** (LB) (LB)	%4-FI %≥ 1:40 (LB) (LB)	%4-FI %≥ 1:40 (LB) (LB)
CSLCT-FLU-05-09 n=1077	48.7 97.8	71.5 99.9 (68.7)	69.7 94.2 (66.9) (92.7)

	(45.6) (96.7)	(99.5)	

CSLCT-NHF-05-11 CSL IVV n=102 Mutagrip n=102	64.7 87.3 (54.6) (79.2) 70.6 89.2 (60.7) (81.5)	93.1 97.1 (86.4) (91.6) 90.2 96.1 (82.7) (90.3)	62.7 72.5 (52.6) **(62.8)** 63.7 76.5 (53.6) **(67.0)**

CSLCT-NHF-05-13 n=60 **	39.0 91.5 **(26.5)** (81.3)	45.8 94.9 **(32.7)** (85.9)	54.2 71.2 (40.8) **(57.9)**
CSLCT-NHF-04-99 n=60 **	55.0 83.3 (42) (71)	90.0 98.3 (79) (91)	56.7 58.3 (43) **(45)**

*for CSLCT-FLU-05-09 Adults ≥18 to <65 years of age
**indicates uncontrolled trial
***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%.
Bold italics indicate failure to meet CPMP criteria.

Table 9-7 Summary of Efficacy in Adults ≥ 65 years of age from post hoc analyses Of all studies submitted to the BLA

Study	A/H1N1	A/H3N2	B strain
	%4-FI*** %≥ 1:40 (LB) (LB)	%4-FI %≥ 1:40 (LB) (LB)	%4-FI %≥ 1:40 (LB) (LB)
CSLCT-NHF-05-15 CSL IVV n=206	34.0 85.0 **(27.5)** (79.3)	44.2 99.5 (37.3) (97.3) 55.9 98.5	45.6 77.7 (38.7) (71.4)
Influsplit n=68	38.2 89.7 **(26.7)** (79.9)	(43.3) (92.1)	39.7 79.4 **(28.0)** (67.9)
CSLCT-NHF-05-11 CSL IVV n=60	40.0 ***58.3*** **(28.6)** **(45.7)**	86.7 91.7 (75.8) (81.9)	41.7 75.0 (30.1) (62.8)
Mutagrip		75.0 91.7 (62.8)	45.0 ***58.3*** (33.1)

n=60	38.3 ***55.0*** **(27.1) (42.5)**	(81.9)	**(45.7)**
CSLCT-NHF-05-13 CSL IVV n=40 **	***10.0*** 65.0 **(4.0) (49.5)**	35.0 100.0 **(22.1)** (91.2)	40.0 70.0 **(26.3) (54.6)**

CSLCT-NHF-04-99 CSL IVV n=37 **	***13.5*** **(5.9)** **(46.1)**	62.2	94.6 100.0 (82.3) (90.6)	***16.2 48.6*** **(7.7)** **(33.4)**

**indicates uncontrolled trial

***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%.
Bold italics indicate failure to meet CPMP criteria for immune response.

• As previously discussed in the Clinical Studies section, while subjects in the supporting non-IND studies were generally successful in meeting CPMP criteria for immune response, all four non-IND studies failed to meet the more stringent immune response criteria set forth by the FDA for one or more of the three vaccine strains. This was true both in Adults ≥ 65 years of age and, to a lesser extent, in Adults ≥ 18 to < 65 years of age.

o For Adults ≥18 to <60 years of age, both CPMP and FDA immune response criteria were fulfilled in the pivotal study CSLCT-FLU-05-09. However, in this same age group, proportion with 4-fold increase in HI titer was not sufficient to meet criteria for both H1N1 and H3N2 in study CSLCT-NHF-05-13, and the proportion of subjects with a post-vaccination anti-HI titer ≥ 1:40 fell short for B strain in studies CSLCT-NHF-05-11, CSLCT-NHF-05-13, and CSLCT-NHF-04-99.

o For Older Adults ≥ 65 years of age, the post hoc analysis of all four non-IND studies demonstrated lower immune responses for the H1N1 strain in particular and B strain to a lesser degree. Neither FDA criteria for proportion with 4-fold increase in HI titer nor for proportion with post-vaccination anti-HI titers ≥ 1:40 were met for the H1N1 strain in studies CSLCT-NHF-05-11, CSLCT-NHF-05-13, and CSLCT-NHF-04-99, or for the B strain in studies CSLCT-NHF-05-13 and CSLCT-NHF-04-99. The CSL vaccine also did not meet FDA criteria for proportion with 4-fold increase in HI titer for the H1N1 strain in study CSLCT-NHF-05-15.

• One possible explanation for these results is that the non-IND studies, particularly the smaller uncontrolled studies, were not powered to demonstrate compliance with the FDA criteria which assess the lower bound of 95% CIs rather than point estimates of effect. The small numbers used in these studies are associated with wide CIs. To explore this possibility further, the applicant pooled data from the two comparator controlled studies. The integrated analysis appears below and is based on the applicant's Table 2.7.3.3-17 in Module 2 Volume 1 Section 2.7.3 p 37:

Table 9-8 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%.

Although the lower bound of the 95% CI for the proportion with 4-fold increase in HI titer for the H1N1 strain is still not >30%, it is improved after increasing the sample size by pooling the data from these two studies, and the proportion of subjects with anti-HI titers ≥ 1:40 is now > 60% for all three strains.

Reviewer comment: Another important consideration regarding the results of the non-IND studies is that the comparator controlled trials also demonstrated lower responses for the H1N1 and B strains among the Influsplit and Mutagrip controls. Results for the H1N1 strain were very similar to CSL IVV. For the B strain, the proportion with 4-fold increase in HI titer for Influsplit and the proportion with anti-HI titer ≥ 1:40 for Mutagrip were both lower than these same parameters in the CSL IVV group. Therefore, it may be somewhat reassuring that although the CSL IVV did not meet endpoints for these strains in the non-IND studies, both a US licensed vaccine, Influsplit (equivalent to Fluarix), and an EU licensed vaccine, Mutagrip, did not meet the same endpoints.

Reviewer comment: There may be still other factors to consider when evaluating the immunogenicity results in Adults ≥ 65 years of age. The applicant sites a quantitative review of 31 immune response studies conducted from 1986 to 2002 in the elderly suggesting that age, previous influenza vaccination, high pre-vaccine titers, and living in an institution may adversely affect the antibody response to vaccination. High pre-vaccination titers may be associated with reduced seroconversion rates and increased proportion with post-vaccination titers ≥ 1:40. Previous vaccination is also associated with reduced seroconversion rates, but appears to have less of an impact on the proportion of subjects with proportion with HI titers ≥ 1:40. The applicant cited limitations in the design of small open-label studies conducted at a single center, changes in vaccine strain, and different degrees of prior exposure to vaccine strains in study populations as contributing to variability in immune response from year to year. Finally, the literature also suggests that humoral immunity wanes in the elderly even after adjusting for vaccine and host factors.

Noting that there was some annual variability in the immune response data collected for annual EU registration for Fluarix (1992-2004), FDA asked the applicant (in a request for information letter dated July 30, 2007) to provide summary immune response data from all studies of CSL IVV in subjects > 60 years of age that were used to support yearly licensure in Europe. The applicant's response (amendment to BLA 125254/0.11 received August 9, 2007) stated that the first study of CSL IVV for annual licensure in the EU was CSLCT-NHF-04-99 conducted in 2005. The only study evaluating immune response for annual registration not already included and reviewed in this BLA is one that was just completed on June 22, 2007 at the Chiltern

Clinical Research Unit in the UK. The applicant provided the following summary table (reproduced from BLA amendment 125254/0.11, p3):

Table 9-9 Study CSLCT-NHF-06-30, 2007/2008 Northern Hemisphere Season Subjects ≥60 years of age

#of participants ≥60 years = 60	%4-fold increase HI % (95%CI)	%post-vacHI≥1:40 % (95%CI)
H1N1 (A/Solomon Islands/3/2006)	73.3 (60.3,83.9)	95.0 (86.1-99.0)
H3N2 (A/Wisconsin/67/2005)	45.0 (32.1,58.4)	98.3 (91.1,100.0)
B strain (B/Malaysia/2506/2004)	38.3 (**26.1**,51.8)	73.3 (60.3,83.9)

This study was not powered to assess FDA immunogenicity criteria of the lower bound of the 95% CI, but if one were to apply these criteria, only one of six, B strain % 4-fold increase in HI titer, did not meet the endpoint. These results demonstrate better immune responses than those from the similarly designed studies CSLCT-NHF-04-99 and CSLCT-NHF-05-13 also conducted for purposes of annual registration in the EU. It is important to note that this table was provided without source data for review. It is only presented here in this review to provide some additional context pertaining to difficulties in interpretation of small immune response studies conducted year to year.

• Finally, the analysis in the age group ≥ 65 years was a post hoc analysis which may have introduced bias or confounding variables making these data difficult to interpret.

• With respect to the pivotal study CSLCT-FLU-05-09, the co-primary endpoints of proportion with 4-fold increase in HI titer and proportion with anti-HI antibody titers ≥ 1:40 were met for all three vaccine antigen strains in healthy Adults ≥ 18 to < 65 years old. In addition, the secondary immunogenicity endpoints of demonstrating lot-to-lot clinical consistency between the three thimerosal-containing multidose vial lots and between each of these and the thimerosal-free pre-filled syringe were fulfilled.

• Due to the limitations in design of the open-label uncontrolled small annual European licensure studies, CSL also conducted studies CSLCT-NHF-05-11 and CSLCT-NHF-05-15 which contained comparison group of licensed influenza vaccines. CSLCT-NHF-05-15 contained a comparison group to Influsplit, the equivalent of U.S. licensed Fluarix. The results of these two studies showed comparable immune responses to the other trivalent inactivated influenza vaccines, including lower immune responses to some of the antigens, for example H1N1. Although the concerns regarding the results of studies -13 and -99 remain, the product will be licensed in all adult age groups with a statement in the label that immune responses were lower among geriatric subjects. Furthermore, post-marketing immune response studies in "at risk" adults will address these issues.

• **Pediatrics**

o FDA did not specifically request immunogenicity data from this pediatric study for formal review in support of the BLA. However, immunogenicity data was included by the applicant in the CSR and is summarized in the table below which is based on the applicant's Tables IV and V pp46-47 Module 5 Vol 26 Section 5.3.5.2-3:

Table 9-10 Applicant's Summary of Immune Responses in Subjects 6 Months to 9 Years of Age, following second dose administered 28 days after first dose, Study CSLCT-FLU-04-05

Strain/ criterion	FDA criteria	Group A ≥6mos to <3yrs	Group B ≥3yrs to <9yrs
		Dose 2 n=139	Dose 2 n=132
H1N1			
% 4-fold increase *	>40%	95.0%	93.9%
% with HI ≥ 1:40**	>70%	95.7%	95.5%
H3N2			
%4-fold increase	>40%	90.6%	70.5
% with HI ≥1:40	>70%	100%	100%
B Strain			
% 4-fold increase	>40%	94.2%	93.2%
% with HI ≥ 1:40	>70%	95.7%	94.7%

*% 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.

Reviewer comment: Both groups of children met all three immunogenicity endpoints after 2 doses of vaccine. The reviewer confirmed these data in the Clinical Trials Section by evaluation of the applicant's line listings.

9.1.5 **Efficacy Conclusions**

• 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-12997.
• With the exception of H1N1 in CSLCT-NHF-05-13 in Older Adults, the four supporting non-IND studies conducted in the UK met CPMP endpoints required for licensure in the EU.
• A post hoc analysis of the four supporting non-IND studies examining subjects ≥65 years of age (n=343) and applying FDA criteria for immunogenicity revealed lower immune responses to both the H1N1 and B strains. We know that immune responses

wane with age, and lower responses in the elderly are not unexpected. In addition, the study analyses are limited by the small sample sizes of the studies which did not have sufficient power to assess criteria based on confidence intervals rather than point estimates. Other host and vaccine-related factors may contribute to the variable immune response from one year to the next as noted above. Nearly identical results were found for the US and EU licensed comparator influenza vaccine controls.

• There is a precedent for approval of Flulaval in the elderly population despite lower immune response results for some strains observed in studies that enrolled subjects ≥65 years of age.

• Other factors which limit our ability to interpret the results of the non-IND studies include the deep subcutaneous route of administration used in the non-IND studies and the HI assay itself which was not validated for the non-IND studies and which was performed at two different laboratories. The deep subcutaneous route is an approved route of administration of influenza vaccine in the EU, and the injections in this study were all given in the region of the deltoid muscle. Although there is insufficient data comparing subcutaneous to intramuscular administration of influenza vaccine in the literature to suggest that these routes of administration might be considered similar, there were no apparent differences in immunogenicity results related to the route of administration in the non-IND studies. Therefore, despite the uncertain effect of the subcutaneous route of administration on immunogenicity, the immune responses elicited by CSL IVV in these studies appeared overall acceptable and, in the reviewer's opinion, support licensure.

• The BLA contained the results of a pediatric study that was a small open-label study conducted in Australia. The 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)], the adult studies relied on a surrogate endpoint for efficacy, and the pediatric study was not controlled for safety. Therefore, at this time the data will not be considered for approval in a pediatric population.

• Despite the lower immune responses found in the elderly in the non-IND studies, CSL IVV is a trivalent inactivated influenza vaccine which has been marketed under different trade names by CSL worldwide since 1968 and which the applicant states has a long tradition of efficacy against natural infection. The antibody responses induced by CSL IVV in the Phase III pivotal trial appear sufficient to reasonably predict clinical benefit in adults ≥18 to <65 years of age with lower responses in the elderly.

• Following accelerated approval, additional studies of CSL IVV will be needed to confirm adequate immunogenicity and protection against infection. In the elderly, approval will be contingent on performing a post-licensure well-designed randomized blinded comparator-controlled study with sufficient power to demonstrate non-inferiority to a traditional US-licensed trivalent influenza vaccine. In addition, a post-licensure culture confirmation study in healthy adults not at increased risk for complications of influenza should be performed with due diligence.

10 Overview of Safety Across Trials

10.1 Safety Database

• Overall Extent of Exposure

o The following tables summarize the overall exposure by study, age group, number of subjects, and thimerosal content. Note that the pivotal study included both thimerosal-containing and thimerosal-free vaccine. The tables are reproduced from the applicant's Table 2.7.4.1.2-1 and Table 2.7.4.1.2-2 Module 2 Volume 2 Section 2.7.4, pp9-10.

Table 10-1 Number of Subjects Receiving Thimerosal-free or reduced CSL IVV In Clinical Studies, 1992-2006

Study	≥18 to <60 years	≥60 years	≥65 years*	Total
CSLCT-FLU-05-09	251	15		266
CSLCT-NHF-05-15		206	206	206
CSLCT-NHF-05-13	60	60	40	120
CSLCT-NHF-05-11	102	104	60	206
CSLCT-NHF-04-99	60	60	37	120
CSLCT-FLU-03-95	60	60		120
CSLCT-FLU-02-86	60	59	35	119
CSLCT-FLU-02-85		106		106
CSLCT-FLU-99-68	80			80
TOTALS (ADULT) Thimerosal-free	763	670	378	**1343**
Pediatric study Thimerosal-free CSLCT-FLU-04-05				**298**

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

Table 10-2 Number of Subjects Receiving Thimerosal-containing CSL IVV in Clinical Studies 1992-2006

Study	≥18 to <60 years	≥60 years	≥65 years*	Total
CSLCT-FLU-05-09	780	43		823
CSLCT-FLU-99-68	80			80
CSLCT-FLU-97-52	99			99
CSLCT-FLU-96-47	103			103
CSLCT-FLU-95-34	101			101
CSLCT-FLU-94-23	97			97
CSLCT-FLU-93-15	94			94
CSLCT-FLU-92-02	100			100
CSLCT-FLU-98-56	85			85
CSLCT-FLU-00-78	80			80
CSLCT-FLU-00-77		59	44	59

CSLCT-FLU-99-67		60	47	60
CSLCT-FLU-98-57		60	45	60
CSLCT-FLU-97-53		70	62	70
CSLCT-FLU-96-48		70	47	70
CSLCT-FLU-95-35		70	58	70
CSLCT-FLU-94-24		70	63	70
CSLCT-FLU-93-16		70	65	70
CSLCT-FLU-92-08		70	44	70
CSLCT-FLU-92-07	100			100
CSLCT-FLU-92-03		64	47	64
TOTALS Thimerosal	1719	706	522	**2425**

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

Table 10-3 Summary: All subjects receiving CSL IVV in Clinical Studies 1992-2006

Group	6mos to<9yr	18 to <60 yrs	≥60 yrs	≥65 yrs*	**TOTAL (applicant summary)**	**TOTAL (reviewer calculations)**
Adults Thimerosal-Free		763	670	378	**1343**	**1433**
Adults with Thimerosal		1719	706	522	**2425**	**2425**
Pediatric Thimerosal-free	298				**298**	**298**
TOTAL (applicant)					**4066**	
TOTAL (reviewer)	**298**	**2482**	**1376**	**900**		**4156**

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

o In summary, the applicant reports a total number of 4066 subjects exposed to CSL's trivalent influenza vaccine in the clinical safety database from 1992 to 2006, including 1376 subjects ≥ 60 years (or 900 subjects ≥65 years) and 298 children. The reviewer found that the total number of subjects exposed was 4156, including 2482 ≥18 to <60, 1376 ≥60 years, 900 ≥65 years, and 298 children. There is a discrepancy between the applicant's and reviewer's numbers which consists of 90 subjects in the group of all adults who received thimerosal-free vaccine as is shown in the above table. This discrepancy appears to have resulted from a clerical error in which two digits in total numbers were

transposed: 1343 instead of 1433.

- Demographics
  - Please refer to Section 9.1.3 of the Efficacy across Trials Overview for a discussion of race, ethnicity, mean age, and gender across the pivotal trial and the four supporting non-IND studies.
  - Regarding the 23 older studies conducted in Australia, the mean ages for Adults 18 to <60 years ranged from 20.9 to 34.6 years, and for Older Adults ≥ 60 years of age ranged from 62.0 to 70.7. The gender ratio was closer to 1:1 in these studies and somewhat different from the gender ratios of the studies submitted to the BLA where females predominated.
  - Clinical studies of CSL IVV have been conducted in healthy adults and older adults. Subpopulations with limited clinical data include persons with immunodeficiency disorders, history of Guillain Barre Syndrome, disease co-morbidities, pregnant females, and children. However, it is likely that persons with disease co-morbidities and other sub-populations have been exposed to the vaccine as a result of wide-spread historical usage and routine vaccination among populations for whom influenza vaccine is indicated. The applicant reports no significant safety issues from post-marketing surveillance which is addressed below.

10.2 Safety Assessment Methods

- Overall, the safety endpoints, methods of collecting data, and statistical analysis were similar across the pivotal and four supporting adult studies allowing us to compare safety data across the five studies in a meaningful way. However, there were some differences between studies CSLCT-FLU-05-09 and CSLCT-NHF-05-15 and the other three supporting adult non-IND studies which are discussed further in this section.
- For the 23 older studies, the applicant reports that similar methods were employed in the collection and analysis of safety data. FDA did not request source data, but asked the applicant to submit an integrated safety analysis from these 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. In general, these studies collected Solicited AEs for 4 to 7 days post-vaccination. Solicited symptoms generally included induration, ecchymosis, temperature, malaise, and shivering. Studies conducted before 1997 did not capture unsolicited AEs, but had more comprehensive Solicited AE diary cards for symptoms such as headache, myalgia, and nausea. Studies conducted after 1997 had an abbreviated Solicited AE card and collected other AEs on that same card for 4 days post-vaccination. This methodology differs from studies CSLCT-FLU-05-09 and CSLCT-NHF-05-15 which had more comprehensive Solicited AE diary cards and which followed Unsolicited AEs to 21 days with the aid of diary cards.
- In order to address safety concerns in the ≥65 years old age group which defines the elderly population in the US, the applicant performed a post hoc age-stratified analysis in this age group for the supporting four non-IND studies and for the 23 older studies.

• The following procedures depicted in Table 10-4 were, in general, common to all 5 main studies submitted to the BLA, pivotal and supporting non-IND adult trials:

Table 10-4 Safety Assessment Methods across Studies Submitted to the BLA

Study	Observation after vaccine	Solicited AE card	Unsolicited AE card	SAE collection	#Unsolicited AEs Reported
CSLCT-FLU-05-09 n=1359	30 min	5 day	21 day	21 day	684
CSLCT-NHF-05-15 n=275	30 min	5 day	21 day	21 day	162
CSLCT-NHF-05-11 n=406	30 min	5 day	5 day	21 day	13
CSLCT-NHF-05-13 n=120	30 min	5 day	5 day	21 day	10
CSLCT-NHF-04-99 n=120	30 min	5 day	5 day	21 day	20
CSLCT-NHF-04-05 n=298	30 min	7 day	30 day	30 day	658

Reviewer comment: Because studies CSLCT-NHF-05-11, CSLCT-NHF-05-13, and CSLCT-04-99 were performed for the purpose of annual registration in the EU, CPMP guidance was followed, and tenderness, headache, myalgia, nausea, and vomiting were not collected as part of the Solicited AEs. However, the applicant states that these symptoms should have been captured in the Unsolicited AEs.

For studies CSLCT-FLU-05-09 and CSLCT-NHF-05-15, Unsolicited AE Diary cards were issued to document AEs for the duration of the study (21 day follow up for each subject). In contrast, for studies CSLCT-NHF-05-11, CSLCT-NHF-05-13, and CSLCT-NHF-04-99, subjects were issued a 4 day Diary card for the collection of both Solicited and Unsolicited AEs. This difference in methodology probably explains why relatively fewer AEs were collected for the older non-IND supporting studies.

10.3 Significant/Potentially Significant Events

10.3.1 Deaths

• No deaths occurred in the pivotal study CSLCT-FLU-05-09 or in the other four supporting non-IND or pediatric studies.
• Only one SAE resulting in death was reported across all 29 clinical studies. This occurred in study CSLCT-FLU-92-03. The applicant provides a narrative in Module 2 Volume 2 Section 2.7.4.7.1d and provides a copy of the original SAE form and the transcribed narrative in Module 5 Volume 29 Section 5.3.7. Details were sent by the study coordinator to the ethics committee:

Subject ID#36: A 74 year old female in Australia with a history of ischemic heart disease, multinodular goiter and rheumatoid arthritis was vaccinated with Fluvax on April 29, 1992. She subsequently suffered a sudden death on May 18, 1992, 2 days after reporting chest discomfort, weakness, and mild GI upset. Cause of death was reported as ischemic heart disease and was not felt to be related to the study vaccine.

10.3.2 Other Significant/Potentially Significant Events

• One SAE occurred in study CSLCT-FLU-05-09. CRF was reviewed:

Subject 27FCI154, a 42 year old female, received CSL IVV multidose vial Lot 1 on July 11, 2006. On July 22, 2006, the subject was the victim on an assault, suffered a fracture of the right femur, and,was hospitalized. She received a tetanus shot on July 23, 2006, and underwent internal fixation of the femur. She was discharged on July 25, 2006 and
subsequently subsequently fully recovered. This SAE was judged not associated with the study vaccine.

• There were no other SAEs or deaths in either the pivotal study or in the five other supporting studies to the BLA.
• A total of 20 SAEs occurred across the older 23 studies and are summarized in the following table:

Table 10-5 Summary of SAEs in 23 Older Studies

SAE	Study	Subject Number	Vaccine	Vaccine-Related
Dehydration/ Diarrhea	CSLCT-04-05	A124	CSL IVV	No
Viral pneumonia Picornavirus	CSLCT-04-05	B087	CSL IVV	No
RSV bronchiolitis	CSLCT-04-05	A013	CSL IVV	No
UTI	CSLCT-04-05	A106	CSL IVV	No

Type I Diabetes	CSLCT-04-05	B063	CSL IVV	No
Death ischemic Heart disease	CSLCT-92-03	36	CSL IVV	No
Fractured femur	CSLCT-05-09	27FCI154	CSL IVV	No
Arrhythmia/ Palpitations	CSLCT-02-86	003	CSL IVV	No
Migraine	CSLCT-02-86	024	CSL IVV	No
Severe abdominal Pain	CSLCT-00-78	04	CSL IVV	No
Mesenteric Adenitis	CSLCT-00-78	04	CSL IVV	No
Esophageal spasm	CSLCT-99-67	19	CSL IVV	No
Myocardial Infarction	CSLCT-98-57	609	CSL IVV	No
Impacted wisdom Teeth	CSLCT-98-56	074	*	No
Knee arthroscopy	CSLCT-97-52	150	**	No
Knee reconstruction	CSLCT-97-52	150	**	No
Elective prostate Surgery	CSLCT- 94-24	531	CSL IVV	No
Myocardial Infarction	CSLCT-94-24	562	CSL IVV	No
Renal calculi	CSLCT-94-23	062	***	No
Perforated peptic Ulcer	CSLCT-93-15	177	Placebo	No

*not specified: Phase IV single blind randomized parallel group placebo controlled as reported in Mod 5 Vol 29 Table A7.3 Sect 5.3.6-8 p30.
**not specified: double blind randomized parallel group placebo controlled
***not specified: double blind randomized parallel group placebo controlled
CSL IVV=CSL's trivalent inactivated influenza vaccine

- There were two other events of special interest which occurred in study CSLCT-NHF-05-09. The CRFs were reviewed:

  - Subject 27FVD137 Serum sickness – described in the safety review section of the study on page 41.

Reviewer comment: it is difficult to know whether this is truly a case of serum sickness. The CRF describes the rash as excoriated papules and urticaria. Ongoing urticaria from July 15, 2006 to April 2007 would be unusual for serum sickness. Results of laboratory investigation, biopsies, or specialist consultation are not provided. Two other cases of serum sickness are reported in the post-marketing experience and will be included in the label, regardless of whether this one case represented a case of true serum sickness.

- Subject 27FVD153 Pregnancy –described in the safety review section of the study on page 41.

• **Review of SAE forms and amendments to IND ----------**

The following safety reports were submitted to CBER under this BB-IND ------- during the annual reporting period April 10, 2006 to April 9, 2007 and during the BLA review period. None of these involved subjects who were enrolled in the pivotal study CSLCT-FLU-05-09

- IND Serial No. 0015, submitted October 18, 2006. A 56 year-old female in the UK, medical history unknown, received influenza vaccine on Nov 7, 2005. She developed encephalitis on Nov 14, 2005 and died on ----------. Autopsy revealed auto-immune non-herpetic acute limbic encephalitis. The patient's physician did not record which vaccine batch or brand the patient received, but the physician's practice used both Solvay Influvax Subunit Batch Number H21 and CSL IVV Batch 0986-01101 (CSL's trivalent inactivated influenza vaccine.) Another patient had been given the Solvay vaccine on the same day as the patient who developed encephalitis. SAE submitted with Amendment 15 to IND ---------- and reviewed.
- IND Serial No. 0017, November 17, 2006. A 65 year-old male patient in Singapore received Fluvax (trivalent inactivated influenza vaccine by CSL) and died 2 hours later. No known allergies, batch number and date of administration unknown. SAE report reviewed. Amendment 17 IND ----------.
- IND Serial No. 0018, Nov 27, 2006. Two reports from the UK in patients who received CSL IVV:
- A 68 year-old male with history of congestive heart failure and chronic renal failure, died 2 days after receiving the influenza vaccine. Batch number 0986-03801, date of administration ----------. SAE report reviewed, Amendment 18 IND ----------.
- A 53 year-old female with history of mental illness attempted suicide, batch number 0986-03701, date of administration unknown. SAE report reviewed. Amendment 18 IND ----------.
- IND Serial No. 0019 and 0028, Nov 30, 2006. A 10-week old premature female in the UK vaccinated with CSL IVV and Palivizumab

developed apnea on the day of vaccination. Recovered the next day. Lot number 05201, date of administration Oct 30, 2006. SAE reports reviewed. Amendments 19 and 28 IND ----------.

- IND Serial No. 0021, Dec 15, 2006. A 65 year old male in the UK was vaccinated with CSL IVV and Pneumovax II on Nov 22, 2006. Five minutes later, he lost consciousness three times, had bradycardia and hypoglycemia. Was treated with oxygen and was recovering at the time of the report. Lot number unknown. SAE reviewed. Amendment 21 IND ----------.
- IND Serial No. 0024, Jan 25, 2007. A 65-year old female from the UK who received CSL IVV on Jan 8, 2007. Developed severe chest pain that same day. History of SVT and cardiac ablation. Lot number unknown. SAE report reviewed. Amendment 24 IND ----------.
- IND Serial No. 0024, Jan 25, 2007. An 81-year old male in Sweden who received Afluria on ----------. Admitted to hospital shortly thereafter (dates not indicated in this report) with fever and pulmonary infiltrates, inflammation or failure. Treated with cefuroxime but worsened and died. Death reported as not being due to the vaccine. SAE report reviewed. Amendment 24 IND ----------.
- IND Serial No. 0026, Mar 26, 2007. From the British Medicines and Healthcare Products Regulatory Agency. An 85-year old female received CSL IVV on Nov 11, 2006, then developed Guillain-Barre Syndrome and died on an unknown date. Cause of death unexplained. SAE report reviewed, Amendment 26 to IND ----------.
- IND Serial No. 0029, Aug 2, 2007. A 54 year old Australian male (DOB --------) without significant previous medical history received influenza vaccination, brand unknown, in June 2005 and was said to develop Guillain Barre syndrome (GBS) in August 2005. The patient's neurologist reported that the patient developed POEMS syndrome, characterized by a paraneoplastic peripheral polyneuropathy, and did not confirm GBS. The neurologist felt that the reaction was very unlikely to be related to influenza vaccine. The patient was treated with immunosuppressants and bone marrow stem cell transplant. SAE report reviewed, Amendment 29 to IND ----------.

Reviewer comment: Although causality is unproven, encephalitis, GBS, and allergic reactions including anaphylaxis should be included in the adverse reactions section of the label.

10.3.3 Dropouts

• There were no withdrawals or discontinuations due to any adverse reaction in study CSLCT-FLU-05-09 or in the five supporting non-IND adult and pediatric studies.

• CSLCT-FLU-05-09 Please refer to Section 8.1.1.2.1 for a complete discussion of the disposition of subjects for this trial. A total of 9 enrolled subjects did not

complete the protocol. Of these, 2 subjects in the placebo group were not vaccinated. All other subjects in the study were vaccinated and included in the Safety Population/analysis. Of the remaining 7 subjects who did not complete the study, but who were vaccinated, 5 were lost to follow-up, 1 withdrew consent, and 1 was withdrawn because source data could not be verified.

• CSLCT-NHF-05-15 All participants completed the study and were included in the Safety analysis. One subject was excluded from the Evaluable pop: Subject 9009 took Leflunomide, a prohibited medication, during the study.

• CSLCT-NHF-05-11 All subjects who were enrolled completed the study. All were included in both the Safety and Evaluable Populations and analyses.

• CSLCT-NHF-05-13 One subject (8017 Adult group) was lost to follow up and did not complete the study. This subject was excluded from the Evaluable Population. All subject who were enrolled were included in the Safety Population and analysis.

• CSLCT-NHF-04-99 All subjects completed the study and were included in the Safety evaluation. One subject (9094 Older Adult group) was excluded from the Evaluable Population because he received a pneumococcal vaccine during the study.

• CSLCT-FLU-04-05 Five subjects were withdrawn before completing the study. Four withdrew consent and one was lost to follow-up. No participant withdrew as a result of an AE.

10.4 Other Safety Findings

10.4.1 Adverse Events Across Trials Submitted to the BLA

• Solicited Adverse Events

The following tables summarize the frequency of local and systemic AE's across trials (based on the applicants tables 2.7.4.2.1a-1 and 2.7.4.2.1a-2, Module 2 Volume 2 Section 2.7.4, pp24-27, and Tables 2.7.4.2.1a-3 Module 2 Volume 2 Section 2.7.4, pp29-31. The applicant's reports were confirmed by review of the electronic datasets.)

Table 10-6 Proportion of subjects with solicited AE's within 5 days post-vaccination in CSLCT-FLU-05-09 and CSLCT-NHF-05-15

	CSLCT-FLU-05-09	CSLCT-NHF-05-15

Adverse Event	CSL IVV Multi-dose n=823 %	CSL IVV Single use n=266 %	Placebo thimerosal n=266 %	CSL IVV n=206 %	Influsplit No thimerosal n=69 %
Age group (years)	≥18 to<65	≥18 to <65	≥18 to <65	≥65	≥65
Swelling	10.0	6.8	0.7	11.2	0
Redness	17.7	12.0	8.2	23.3	8.7
Pain	37.4	47.0	9.3	8.7	0
Tenderness	57.1	68.0	17.9	33.5	17.4
Bruising	5.1	3.8	1.1	4.4	1.4
Fever ≥37.7ºC (99.86ºF)	1.1	1.5	0.7	1.0	1.4
Headache	25.2	27.1	25.7	14.6	10.1
Malaise	18.8	21.4	18.7	9.7	7.2
Myalgia	12.2	15.0	9.0	14.1	10.1
Chills/ Shivering	3.3	2.3	2.2	6.8	5.8
Nausea	5.7	8.6	8.6	3.4	2.9
Vomiting	0.9	0.8	0.7	0	0

CSL IVV=Afluria or CSL IVV, CSL's trivalent inactivated influenza vaccine

Reviewer comment: There appeared to be a greater proportion of subjects who experienced injection site pain and tenderness, headache and malaise among CSL IVV recipients than in the Influsplit group, and among younger subjects as compared with older adults. The majority of these events were mild or moderate, with few severe in intensity.
These reactions are considered to be related or caused by the study vaccine.

Table 10-7 Proportion of Subjects with Solicited AEs within 4 days post-vaccination. Post hoc integrated analyses of CSLCT-NHF-05-11, CSLCT-NHF-05-13, CSLCT-NHF-04-99 stratified by age <65 and ≥65 years

	Integrated totals: CSLCT-NHF-05-11, CSLCT-NHF-05-13, and CSLCT-NHF-04-99			
	≥18 to <65 years		≥65years	
Adverse Event	CSL IVV n=309 %	Mutagrip n=140 %	CSL IVV n=137 %	Mutagrip n=60 %

Induration ≥50mm	1.0	2.1	1.5	1.7
Induration ≥50mm x 3 days	0.0	0.0	0.0	0.0
Ecchymosis	5.8	6.4	6.6	6.7
Erythema	16.8	20.0	10.2	11.7
Pain	30.1	21.4	11.7	3.3
Malaise	10.0	10.0	0.7	3.3
Fever >38ºC ≥24hr	0.7	0.7	1.5	1.7
Chills	2.9	2.9	0.7	1.7

Reviewer comment: The symptoms monitored for these studies were fewer and differed slightly than for the pivotal and older adult studies. The proportion of subjects experiencing each symptom was generally similar between CSL vaccine compared with Mutagrip within age group, but there appeared to be more erythema, pain, and malaise in the younger adults than in adults ≥65 years of age in both treatment groups. Reactogenicity events were not graded for severity in these studies. These reactions considered to be vaccine-related.

• **Unsolicited Adverse Events**

o The following table summarizes Unsolicited AEs occurring in ≥3.0% of subjects in controlled trials CSLCT-NHF-05-09, CSLCT-NHF-05-15 and CSLCT-NHF-05-11.

o Based on the applicant's Table 32 Module 5 Volume 1 Section 14 pp270-281; Table 8.1 Module 5 Volume 14 Section 14.3.1 pp177-179; and Table 9.1 Module 5 Volume 17 Section 14, pp160-161.

o Applicant's numbers were confirmed by review of the electronic datasets.

Table 10-8 Summary of Unsolicited AEs Occurring in ≥3.0% of Subjects in any Treatment Group for Controlled Trials submitted to the BLA

Preferred term	CSLCT-NHF 05-09		CSLCT-NHF-05-15		CSLCT-NHF-05-11
Age group (years)	18 to≤65	≥65	≥18 TO <60	≥60	

	CSL IVV n=1089 %	CSL IVV n=206 %	Influ-split n=69 %	CSL IVV n=102 %	Muta-grip n=102 %	CSL IVV n=104 %	Muta-Grip n=98 %
Headache	**7.5**	**8.3**	**7.2**	0	1.0	1.0	1.0
Reactogenicity Event	3.2	2.4	2.9	*	*	*	*
Nasal congestion	0.7	**6.8**	2.9	*	*	*	*
Rhinorrhea	0.7	**5.3**	1.4	0	0	0	1.0
Pharyngolaryngeal Pain	3.0	4.9	2.9	*	*	*	*
Cough	0.7	**5.3**	1.4	*	*	*	*

CSL IVV=Afluria or CSL IVV, CSL's trivalent inactivated influenza vaccine
Percentages refer to the number of subjects with an AE
*Data not presented in applicant's tables/datasets apparently because the AE was not reported by any subjects.

- Unsolicited AEs experienced by >5% of CSL IVV recipients across the controlled trials submitted to the BLA are highlighted in bold print and included: headache, nasal congestion, rhinorrhea, and cough. There appeared to be more nasal congestion, rhinorrhea, and cough among CSL recipients than in the comparator group in Study CSLCT-NHF-05-15.

Unsolicited Adverse Events in Subjects ≥65 years of age from Post Hoc Analysis of non-IND studies submitted to the BLA

- The sponsor did not provide post-hoc integrated data for unsolicited adverse events in the non-IND studies for the population ≥ 65 with the original BLA submission, but at FDA's request, supplied this information in Amendment 125254/0.4 dated June 13, 2007. The following data is based on that information:

Table 10-9 Integrated Post-hoc Analysis of Unsolicited AEs occurring in ≥3% of subjects ≥65 years of age from non-IND studies submitted to the BLA

System Organ Class Preferred Term	Totals, all 4 studies (integrated)			
	CSL IVV n=343 %	Influsplit n=69 %	Mutagrip n=60 %	

Respiratory, thoracic, &mediastinal disorders Nasal congestion Rhinorrhea	**9.0** 4.1 3.2	**10.1** 2.9 5.8	**0.0** 0.0 0.0
Nervous system disorders Headache	**6.1** 5.5	**8.7** 7.2	**1.7** 1.7

Gastrointestinal disorders	**2.9**	**4.3**	**0.0**
Musculoskeletal and connective tissue disorders *	**3.2**	**1.4**	**1.7**
Infections and infestations	**2.9**	**1.4**	**0.0**
General disorders and administration site conditions	**1.5**	**2.9**	**0.0**
Eye disorders	**0.9**	**0.0**	**0.0**
Skin and subcutaneous tissue disorders	**0.3**	**2.9**	**0.0**
Injury, poisoning and procedural complications	**0.9**	**1.4**	**0.0**
Ear and labyrinth disorders	**0.9**	**0.0**	**0.0**
Surgical and medical procedures	**0.3**	**0.0**	**0.0**
Investigations	**0.3**	**0.0**	**0.0**
Renal and urinary disorders	**0.3**	**0.0**	**0.0**
Vascular disorders	**0.3**	**0.0**	**0.0**
Psychiatric disorders	**0.0**	**1.4**	**0.0**
Reproductive system and breast disorders	**0.0**	**1.4**	**0.0**
Immune system disorders	**0.0**	**1.4**	**0.0**
Cardiac disorders			

% based on number of subjects in the respective groups
For some System Organ Classes, there were no AEs/preferred terms which occurred in ≥3% of subjects
CSL IVV=CSL's trivalent inactivated influenza vaccine

Reviewer Comment: Overall, unsolicited AEs in these studies were infrequent. The most commonly reported preferred terms by CSL vaccine recipients were headache (5.5%), nasal congestion (4.1%), and rhinorrhea (3.2%). Study CSLCT-NHF-05-15 was disproportionately represented relative to the other non-IND studies in this summary because of the greater number of subjects (206 out of 343, 60%) and because unsolicited AEs were reported for 21 days post-

vaccination as opposed to 3 days post-vaccination in the other three studies.

- **23 Older Studies**

- **Thimerosal-containing versus Thimerosal-free vaccine**

10.4.13 Post-marketing Experience

o Please refer Section 8.1.6 which reviews the integrated safety summaries provided by the applicant for subjects ≥65 years of age, one for the non-IND studies (CSLCT-NHF-05-15, CSLCT-NHF-05-11, CSLCT-NHF-05-13, and CSLCT-NHF-04-99) and one for the 23 older Australian studies.

o Pain, warmth, and erythema at the injection site were the most common local reactions while headache, malaise, and myalgia were the most common systemic reactogenicity events.

o Review of unsolicited events in both adult and older adults revealed mostly mild to moderate events, low in frequency, with no unexpected patterns attributable to the CSL IVV. Most common events were coincidental upper respiratory infection, headache, seasonal allergic rhinitis, and diarrhea.

o No unexpected patterns were noted.

- **Pediatric study**

The most common Solicited AEs in both the younger (≥3 months to <3 years) and older (≥3 years to <9 years) were pain and redness at the injection site and rhinitis and irritability, mostly mild to moderate in severity.

A total of 658 unsolicited AEs were recorded, 388 in the younger age group and 270 in the older group. Most were mild or moderate in severity. Most frequent were flu-like symptoms, but all throat swabs were negative for influenza A and/or B.

o Serum sickness: the applicant reports three spontaneous reports of serum sickness associated with both thimerosal-containing and thimerosal-free product. However, they cite insufficient evidence for the diagnosis or causality. A case of serum sickness was suspected in the pivotal study, CSLCT-FLU-05-09, and is summarized both in the review of that trial (Section 8.1.1) and in Section 10.3.2

above.

- Deaths
  - The applicant reports only one death reported across 29 studies. A copy of the original SAE form and the transcription of the narrative is provided for subject #36, study CSLCT-FLU-92-03, and is reviewed in Section 10.3.1 above, deaths associated with clinical studies.

10.5 Safety conclusions

- CSL has been manufacturing trivalent inactivated influenza vaccine by essentially the same process since 1968 except for eliminating thimerosal in 2002. Since 1968 it has distributed approximately 24 million thimerosal-containing doses and 23 million thimerosal-free doses worldwide. The applicant reports 4066 subjects in its cumulative clinical study database (4156 per reviewer's calculations), 1089 of which were adults enrolled in the pivotal study submitted to the BLA.
- There has been only one SAE resulting in death across all 29 clinical studies. No deaths or SAEs were reported among CSL IVV recipients in the pivotal study nor in the five supporting non-IND studies submitted to the BLA. There have been 20 reported SAEs across the 23 older clinical studies conducted in Australia, all judged unrelated to the study vaccine. No unusual patterns or safety signals are noted.
- There were no discontinuations or dropouts due to any AE in the pivotal or five non-IND studies submitted to the BLA. Most common solicited AEs across these studies were injection site pain, tenderness, erythema, headache and malaise, and were mostly mild to moderate in severity. Unsolicited AEs were relatively few in number, primarily flu-like symptoms, mild to moderate in severity, with no unusual or unexpected patterns.
- Study CSLCT-NHF-05-15 and the post hoc integrated age-stratified analyses of subjects ≥65 years of age (n=345 from the four non-IND studies submitted to the BLA) do not raise safety signals peculiar to this age group.
- The pediatric clinical trial (n=298) and post marketing experience is small, and safety concerns were not identified.
- There do not appear to be differences in the safety data between subjects who have received thimerosal-containing versus thimerosal-free vaccine in the controlled randomized study.
- The broad post-marketing experience has included monitoring children, pregnant females, SAEs, serious neurologic and immune disorders, and deaths, and has not raised any significant safety issues. Rare cases of transverse myelitis, GBS, and serum sickness have been reported and should be mentioned in a post-marketing section of the label although causality in unproven.
- A limitation of the pivotal and supporting studies is the collection of safety data for 21 days following vaccination. The exception to this is the pediatric study in which SAEs were reported for 6 months following vaccination, and there were no important safety concerns identified in this study.
- The applicant should continue its post-marketing surveillance. Approval of the US license application will be contingent upon a commitment from the applicant to conduct a post-licensure study in children, healthy adults 18 to < 65 years of age, and in adults 65 years of age and older and/or adults with chronic medical conditions

placing them at risk for complications of influenza disease. Safety data should be collected for 6 months following vaccination. An updated Pharmacovigilence Plan will eventually be submitted with an application for traditional approval as a supplement to the BLA.
• Overall, the methodology, integrity of data, and results of safety data presented by the applicant support approval of the BLA.

11 Additional Clinical Issues

11.1 Directions for Use, Dosing, and Administration

- Afluria (CSL IVV) will be supplied as a sterile suspension for intramuscular injection in two presentations:
  - 0.5 mL preservative-free formulation in a 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.
  - Each 0.5mL dose contains 15 mcg of influenza virus HA of each of the three strains: A/Solomon Islands/3/2006 (H1N1); A/Wisconsin/67/2005 (H3N2); and B/Malaysia/2506/2004.
- Dosage in adults is a single 0.5mL intramuscular injection in the deltoid region of the upper arm.

11.3 Special Populations

- Demographic data gathered in the analysis of the studies included age, gender, race/ethnicity, and prior year influenza vaccination. Gender and race/ethnicity are not known to influence the humoral immune response, while age and previous influenza immunization may affect this response.

- For the pivotal study CSLCT-FLU-05-09, the mean age of subjects in the evaluable population was 38 years. Between 43% and 51% had received influenza vaccination in the previous flu season 2005-2006. 37.5% of subjects were male and 62.5% were female. The racial/ethnicity demographic was representative of the US Census in 2000 but with some over-representation of Caucasions (81% versus 75%) and under-representation of Hispanics (2-5% versus 12%). Race/ethnicity data was not collected for the UK studies, but the UK population is generally less diverse, with a higher proportion of Caucasians than in the US. The demographics of Slough, UK also had more Asians relative to the US census data.

- **Geriatrics**

The BLA provided immunogenicity and safety source data for 343 subjects ≥65 years of age across four non-IND studies. In addition, the applicant provided integrated safety data from 23 older Australian studies which included 557 subjects ≥65 years of age. While the total safety population of 900 subjects in this age group is insufficient to detect a rare adverse event, when viewed in the context of the total safety database of 4,066 (4,156 per reviewer's calculations) subjects across 29 clinical studies since 1992 and a

large post-marketing surveillance experience since 1985, the safety profile in this age group appears to be acceptable at this time.

With respect to the surrogate endpoints of immune response, the results of studies CSLCT-NHF-05-15 and CSLCT-NHF-05-11 (n=266) are acceptable and likely to predict clinical benefit. Studies CSLCT-NHF-05-13 and CSLCT-NHF-04-99 (n=77) found lower immune response results among subjects ≥65 years of age, but the small sample size, known weaker immune responses in the elderly, and potential differences in routes of administration make these results difficult to interpret. At FDA's request, the applicant provided a summary of immune response data from the most recent study conducted for annual licensure in the EU. In this uncontrolled open-label study, CSLCT-NHF-06-30 conducted at the same site in the UK as the other non-IND studies and completed June 22, 2007, 60 adults, 60 years of age or older, met CPMP criteria for each vaccine strain. Five of the six immune response criteria set forth in the FDA guidance document were met in this age group.

Overall, considering the risk benefit profile of this product, it appears reasonable to extend accelerated approval to the geriatric population conditional upon the commitment to perform post-marketing studies to confirm safety and efficacy.

• **Pediatrics**

The Pediatric Research Equity Act 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 applicant submitted one pediatric study of 298 children to the BLA that was not originally designed to support U.S. licensure, but rather, to evaluate the safety and immunogenicity of the 2005/2006 formulation for the Swiss regulatory authority in support of a pediatric indication. The data were submitted to the BLA to enhance the safety database. Overall, the safety profile was similar to that in adults, with mild to moderate expected reactogenicity events, and no serious or unusual vaccine-related unsolicited events. The secondary surrogate immunogenicity endpoints demonstrated acceptable immune responses after the second dose of vaccine.

The BLA contained the results of a pediatric study that was a small open-label study conducted in Australia. The 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)], the adult studies relied on a surrogate endpoint for efficacy, and the pediatric study was not controlled for safety. Therefore, at this time the data will not be considered for approval in a pediatric population.

12 Conclusions – Overall

o Afluria (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 under BB-IND- ----------. The four supporting non-IND studies conducted in the UK met CPMP endpoints required for licensure in the EU. The antibody responses induced by Afluria in the Phase III pivotal trial and in the larger non-IND trials appear sufficient to reasonably likely to predict clinical benefit in adults ≥18 to <65 years of age.

o A post hoc analysis of the four supporting non-IND studies examining subjects ≥65 years of age and applying FDA criteria for immunogenicity revealed low immune responses to both the H1N1 and B strains. These analyses are limited by the small sample sizes of the studies which did not have sufficient power to assess criteria based on confidence intervals rather than point estimates. Nearly identical results were found for the US and EU licensed comparator controls.

o Weak immune responses among an elderly cohort are not unique to CSL IVV. Flulaval was granted accelerated approval despite failure to meet immunogenicity endpoints in the H1N1 and B strains. In addition, Fluarix has demonstrated some variability in immune response for all three vaccine strains in studies conducted annually for purposes of yearly EMEA licensure (data presented in the pre-IND Meeting Briefing Document from GlaxoSmithKline for Fluarix clinical development, 22 October 2004). Finally, Fluzone was used as a comparator control to an experimental cell-based influenza vaccine (IND ---------- Amendment number 7, 13 August 2007), and elicited weak immune responses to H1N1 and B strain in the elderly cohort. In contrast, as noted in Section 11.3, Special Populations, the applicant's most recent open-label study conducted for annual registration in the EU, CSLCT-NHF-06-30, met CPMP point estimates and five of the six FDA criteria for immune response.

o Other factors which limit our ability to interpret the results of the non-IND studies include the route of administration and the lack of validation of the HI assay for the non-US IND studies. The route of administration in the non-IND studies was either intramuscular or deep subcutaneous, a practice which is widely accepted in the European Union. It is unclear how the deep subcutaneous route of administration affects immunogenicity, but there was no obvious difference in immune response between subjects who received vaccine by this route as opposed to the intramuscular route in the controlled studies. Furthermore, Fluarix was approved in the geriatric population based on European studies which allowed administration by either route, and used HI assay results that were not validated for non-US IND studies of Fluarix.

o Deaths or serious adverse events were very infrequent in the overall safety database. The adverse event profile seems to be very similar to other licensed inactivated trivalent influenza vaccines. A limitation of the pivotal and supporting studies is the collection of

safety data for only 21 days following vaccination, except for the pediatric study in which SAEs were reported for 6 months following vaccination. However, CSL has been manufacturing trivalent inactivated influenza vaccine by essentially the same process since 1968 except for eliminating thimerosal in 2002. Since 1968 approximately 24 million thimerosal-containing doses and 23 million thimerosal-free doses were distributed worldwide. The applicant reports that 4066 subjects have been enrolled in studies that evaluated safety in a prospective manner. Furthermore, there are post-marketing safety experiences in other countries. Overall, the methodology, integrity of data, and results of safety data presented by the applicant support approval of the BLA.

13 Recommendations

13.1 Approval

o It is recommended that Afluria be approved for the indication of active immunization of persons age 18 years and older against influenza disease caused by influenza virus types A and B present in the vaccine.

13.2 Recommendations on Postmarketing Actions

o In a telecon between CSL and FDA on August 9, 2007, the applicant agreed to conduct four postmarketing studies. Detailed synopses or drafts of all four protocols are to be submitted to both IND ------- and to the BLA by August 31, 2007.
o Clinical Endpoint Efficacy Study: will be a placebo-controlled trial in healthy adults in whom vaccination is not universally recommended to be initiated March 2008 and completed August 2008 in the Southern Hemisphere. Planned CSR Q2 2009. The primary endpoint will be culture confirmed influenza illness. If the influenza attack rate is lower than expected, participant enrollment will be extended to a second season.
o At-Risk Adult Study: will be a non-inferiority immunogenicity study in adults ≥18 years of age who have chronic medical conditions placing them at risk for complications of influenza or who otherwise fall into groups for whom vaccination is recommended. The comparator control will be a U.S. licensed trivalent inactivated influenza vaccine (TIV). The study will begin in August 2008 and end in September 2008 in the Northern Hemisphere.
o Pediatric Studies: there will be two pediatric studies. The Pediatric Open-Label Study will begin March 2009 and end June 2009. The Pediatric Non-inferiority Study will begin August 2009 and end September 2009, and will compare CSL IVV to a U.S. licensed TIV control.
o The final post-marketing commitments are listed in Appendix 1.

13.3 Labeling

o Labeling negotiations were completed in September 2007 before the approval. Major changes to the applicant's original label include the following:

Changes were made in accordance with the new Physician's Labeling Rule and to harmonize the label with other trivalent inactivated influenza vaccine labels which have been granted accelerated approval.

A single package insert was used for both the single-dose syringe and the multi-

dose vial presentations.

A statement was added to the Indications and Usage section reflecting the absence of controlled clinical studies demonstrating a decrease in influenza disease after vaccination with Afluria.

"Life-threatening reactions to previous influenza vaccination" was added to the contraindications.

The Warnings and Precautions section was divided into subsections. Practice of medicine statements such as "never administer by intravascular injection" and some detailed discussion of Guillain Barre Syndrome were deleted. A warning that vaccination may not protect all individuals was added.

Adverse reactions were revised to note that SAEs were limited to the post-marketing experience as opposed to the more common AEs observed in clinical trials. Text from the safety experience section was made more concise. Tables were simplified for ease of understanding, for example, results of the single-dose syringe and multi-dose vial groups were combined into a single CSL influenza vaccine (CSL IVV) group. Percentages in the Unsolicited AE table were changed to reflect the proportion of subjects rather than proportion of all AEs as was done for Solicited AEs. Note was made that solicited and unsolicited AEs were "mostly" and not "only" mild or moderate. Serum sickness and transverse myelitis were added to the post-marketing experience.

Drug interactions were modified to add that there are no data to assess the concomitant administration of Afluria with other vaccines.

Use in pregnancy was modified to state that it is not known whether Afluria can cause fetal harm or can affect reproductive capacity, and should be given only if clearly indicated. The absence of data regarding excretion of Afluria in human milk was added.

Use in pediatrics was changed to state that the safety and effectiveness of Afluria has not been established in persons less than 18 years of age.

Use in geriatrics was modified to make note of lower immune responses in these subjects.

Description of Afluria was changed to note its color, sediment, and suspension qualities. Salts were eliminated from the description. The specific quantities of thimerosal and certain residual substances such as ovalbumin and antibiotics were added. A statement was added to note that both presentations of Afluria are latex-free.

The Clinical Pharmacology section was expanded for harmonization with other trivalent inactivated influenza vaccine labels.

Clinical Studies

"seroprotection" was replaced with proportion or % with HI antibody titer ≥1:40.

Table 3 Study 1 was simplified to combine all CSL IVV vaccinees into one group.

The GMT fold increase column was eliminated from Table 4 Study 2. The table and text were moved to follow the pivotal study. Text indicating that the co-primary endpoints were met was eliminated as this referred to point estimates. FDA criteria for immune response were retained in the footnotes to the table.

Table 5 Study 3 was eliminated and text added to describe the results. The age group stratification was changed from 18 to less than 60 years and ≥60 years used in the prespecified analysis to 18 to less than 65 years

and ≥65 years used in the post hoc analysis. The results were reported in the context of FDA criteria for immune response and included the results of the post hoc analysis. Note was made of the lower immune responses in the elderly subjects and of the similar results in the EU-licensed active control group.

Patient Counseling Information was changed to indicate that: the vaccine does not cause influenza; full effect is achieved approximately 3 weeks (not 2-3 weeks) after vaccination; and that annual revaccination is recommended. A statement that protection is usually maintained for 6-12 months was eliminated. Also deleted were statements relating to information materials for parents/guardians and instructions to notify parents or guardians of the presence of thimerosal.

Appendix 2 contains the final label.