BLA Number: 125297

Related IND Numbers: -b(4)----

Reviewer Name, Division, and Mail Code:

Clinical Reviewer: Melisse Baylor, MD. CBER/OVRR/DVRPA/Clinical Trials Branch, HFM-475
Supervisory Reviewer: Douglas Pratt, MD, MPH. Branch Chief, CBER/OVRR/DVRPA/Clinical Trials Branch, HFM-475

Submission Received by FDA: July 11, 2008

Review Completed: December 2, 2009

PRODUCT

Proper Name: Influenza virus vaccine
Proposed Trade Name: Agriflu
Product Formulation:

The 2008-2009 vaccine contains hemagglutinins (HA) from three influenza strains (total HA = 45 µg)

A/Solomon Islands/3/2006 (H1N1):	15 µg
A/Wisconsin/67/2005 (H3N2):	15 µg
B/Malaysia/2506/2004:	15 µg

Agriflu contains the following excipients: ---b(4)---------- and trace amounts of formaldehyde, kanamycin, neomycin -b(4)--, polysorbate 80, and cetyltrimethylammonium bromide

No adjuvant is included in this vaccine. There are no preservatives in Agriflu.

Applicant: Novartis Vaccines and Diagnostics, Incorporated (heretofore called applicant or Novartis)
Pharmacologic Class or Category: Vaccine
Proposed Indication: Active immunization of persons 18 years of age and older against influenza disease caused by influenza caused by influenza virus types A and B contained in the vaccine
Proposed Population: Adults 18 years of age and older
Dosage Form and Route of Administration: Agriflu is supplied in a single-dose 0.5 mL prefilled syringe to be administered by intramuscular injection

2. Table of Contents

3. Executive Summary

3.1 Recommendation on Regulatory Action

In the opinion of the clinical reviewer, the data submitted by the Applicant support the approval of the trivalent inactivated influenza vaccine Agriflu for active immunization of adults 18 years of age and older against influenza disease caused by influenza subtypes A and type B contained in the vaccine. The recommendation for accelerated approval of Agriflu is based on its effect on a surrogate endpoint that is reasonably likely to predict that patients will derive clinical benefit from Agriflu. Two randomized, active-controlled studies showed that subjects who received Agriflu had immune responses that successfully met the six pre-defined criteria for influenza A and B. The safety profile of Agriflu was similar to that of Fluvirin, which is licensed in the United States and was the active control in the two pivotal studies. Although an inspection by CBER's Bioresarch Monitoring Branch (BIMO) revealed multiple irregularities in safety monitoring at the study sites for one of the two pivotal trials, safety data were also provided from ten additional studies of Agriflu. The adverse events observed most commonly after vaccination with Agriflu were pain at the injection site, headache, myalgia, and malaise. There were no individual safety concerns or patterns of safety concerns associated with the administration of Agriflu, and the safety data provided in this application are adequate to support the conclusion that Agriflu is safe for use in adults 18 years of age and older. Therefore, the potential benefits of administration of Agriflu outweigh the potential risks. With this accelerated approval, the availability of an additional trivalent influenza vaccine provides meaningful benefit in the current setting of a shortage of influenza vaccine supply to adequately immunize all persons for whom the CDC recommends annual vaccination.

3.2 Recommendation on Postmarketing Action

The Applicant has agreed to submit the results of Study V58P13, a Phase 3, randomized, observer-blind, placebo-controlled, clinical endpoint study to assess the vaccine efficacy of Agriflu. This study was conducted in the 2007-2008 influenza season. The applicant has also agreed to conduct two randomized, observer-blind, active controlled, immunogenicity studies in pediatric subjects; Study V71_18 will be conducted in children from 3 years to 17 years of age and Study V71_20 will be conducted in children from 3 months to 35 months of age. The applicant has also agreed to conduct a non-inferiority immunogenicity study with Agriflu and a US-licensed trivalent inactivated seasonal influenza vaccine in a population of adults 50 years of age and older. Finally, the Applicant has agreed to establish a pregnancy registry to prospectively collect data on spontaneously-reported exposures to Agriflu during pregnancy.

3.3 Summary of Clinical Findings

The conclusions about the safety and immunogenicity of Agriflu were based on the safety and immunogenicity results from two pivotal trials, three additional studies to support immunogenicity, and 11 additional studies to support safety. The two pivotal trials were randomized, observer-blind, controlled studies in a combined total of 2185 healthy adult volunteers from 18 to 64 years of age. The three studies submitted in support of immunogenicity enrolled 4077 healthy adult volunteers, while the 11 additional studies to support safety enrolled 1831 adult volunteers.

The immunogenicity of Agriflu in the two pivotal trials was measured by endpoints and criteria described in the FDA Guidance for Industry, "Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines." The two endpoints were: 1) proportion of subjects with seroconversion at Day 21 (four fold rise in hemagglutination inhibition (HI) titers or change from undetectable to a titer of ≥ 1:40) and 2) proportion of subjects achieving a HAI titer ≥ 1:40 at Day 21. Responses for these endpoints were measured against pre-defined criteria for these two endpoints as described in the Guidance. The criteria for seroconversion were ≥ 40%, and the criteria for percentage of subjects achieving HAI titers ≥ 1:40 22 days post-vaccination were ≥ 70%. The results are shown in the following table.

Table 1: Hemagglutination-Inhibiting (HAI) Antibody Responses to Agriflu in the Two Pivotal Clinical Trials

	Study V71P5 N=424 18-64 Years of Age			**Study V71P6 N=1182 18-49 Years of Age**		
	A/H1N1	**A/H3N2**	**B**	**A/H1N1**	**A/H3N2**	**B**
Seroconversion Rate	74%	72%	77%	94%	67%	84%
LL 95%CI*	69%	68%	72%	93%	65%	82%
% of Subjects with HI≥1:40 Post-Vaccination	93%	96%	91%	98%	99%	87%
LL 95%CI*	90%	94%	87%	97%	98%	85%

*LL 95% CI is the lower limit of the 95% confidence interval.
Source: BLA 125297, CSRs, Table 11.4.1.1-1, page 66 and Table 11.4.1.2.1-1, page 50

The results for the proportion of subjects with seroconversion and the results for the proportion of subjects with HAI titers ≥ 1:40 post-vaccination met the target criteria for both influenza A strains and for the influenza B strain.

The results of three studies were submitted to demonstrate the immunogenicity of Agriflu; these studies were designed to satisfy the yearly criteria for strain changes as recommended by Committee for Proprietary Medicinal Products [(CPMP). Note for guidance on harmonization of requirements for influenza vaccines. CPMP/BWP/214/96. The European Agency for the Evaluation of Medicinal Products (EMEA), March 1997]. All three of these trials were

randomized, observer-blind studies in which Agriflu was the active control for an experimental cell-derived seasonal influenza vaccine. As shown in the table below, the results of two of these studies satisfied both the criteria recommend by the CPMP and those recommended by CBER.

Table 2: Point Estimates (Lower Bound 95% Confidence Interval) for HI Titers in Supportive Immunogenicity Studies of Agriflu (Studies 58P4 and V58P9)

	18-60 Years of Age		**≥61 Years of Age**
	V58P4 N=644	**V58P9 N=168**	**V58P4 N=674**
Seroconversion Rate			
H1N1	67% (63%)	77% (70%)	55% (51%)
H3N2	64% (60%)	88% (82%)	65% (61%)
B	81% (78%)	70% (63%)	73% (70%)
Post-Vaccination % of Subjects with HI Titers≥1:40			
H1N1	92% (89%)	95% (91%)	85% (82%)
H3N2	99% (98%)	96% (92%)	98% (97%)
B	91% (88%)	88% (82%)	89% (87%)

Source: BLA 125297, CSR, Tables 11.4.1.1-1 – 14.1.1.-3 and 11.4.1.2-1 – 1.4.1.2-3 pages 80-85, and Tables 11.4.1-2 – 14.1-4 pages 72-76

As in the pivotal trial, in the supportive studies, the results for the percentage of subjects with seroconversion and the percentage of subjects with HI titers of 1:40 or greater after vaccination with Agriflu met the target CBER criteria for both influenza A strains and for the influenza B strain.

The results of a third study, V58P2 were submitted at the request of CBER. This study was similar in design to Study V58P4, but was a smaller study conducted in a study population in which a large percentage of subjects had previously been vaccinated against influenza. The results of this study are shown in the table below.

Table 3: Study V58P2 – Point Estimates (Lower Bound 95% Confidence Interval) for HI Titers in Subjects by Age Cohort

Influenza Strain	18-60 Years of Age N=57	≥61 Years of Age N=56
Seroconversion Rate		
H1N1	37% (24%)	13% (5%)
H3N2	30% (18%)	13% (5%)
B	28% (17%)	30% (19%)
Post-Vaccination % of Subjects with HI Titers≥1:40		
H1N1	79% (66%)	75% (62%)
H3N2	96% (88%)	93% (83%)
B	39% (26%)	38% (25%)

Source: BLA 125297, CSR, Tables 11.4.1.1-1 – 14.1.1.-3 and 11.4.1.2-1 – 1.4.1.2-3 pages 69-84

As shown above, the seroconversion rate for all three strains and in both age groups did not meet the criteria described in the FDA Guidance for Industry. The percentage of subjects with post-vaccination titers of 1:40 or higher did meet the criteria for the influenza A/H3N2 strain in both age groups, but the percentage of subjects with post-vaccination titers of 1:40 or higher did not meet the criteria for the other two influenza strains. The reason for the poor outcome in this study is unclear but may be related to the high percentage of subjects who had been previously vaccinated. However, the percentages of subjects in Study V58P2 with baseline HI titers of 1:40 or greater was not substantially different from the percentages reported for subjects in Studies V71P5 and V71P6. It also must be noted that this study was designed to satisfy criteria used by the EMEA and was not designed to support licensure in the United States or to meet the criteria for demonstrating immunogenicity as described in the FDA Guidance.

In the opinion of this reviewer, the results from the two pivotal studies and the two supportive studies support the immunogenicity of Agriflu.

The primary support for the safety of Agriflu came from the two pivotal studies, V71P5 and V71P6, which were randomized, observer-blind studies comparing Agriflu to Fluvirin in healthy adult volunteers. A total of 692 adults from 18 to 64 years of age were randomized and vaccinated in Study V71P5; 1493 adults 18 to 49 years of age were randomized and vaccinated in study V71P6. A BIMO inspection revealed multiple irregularities in safety monitoring at the study sites in V71P6; however, safety data from multiple other studies were submitted in the BLA. These additional studies were 1) six European annual re-registration studies, 2) three studies comparing thimerosal-free and thimerosal-reduced formulations, 3) a re-vaccination study of subjects in V58P4, and 4) a pilot study conducted at a new study site.

The safety assessments in the studies were similar. Solicited adverse reactions were collected for the day of vaccination and for the six subsequent days in the two pivotal trials and for the day of

vaccination and the three subsequent days in the supportive trials. Unsolicited adverse events were followed for the 21 days post-vaccination. Information on serious adverse events was collected for the entire study period of each study, which ranged from 22 to 180 days post-vaccination.

The adverse events observed most commonly in the seven days after vaccination with Agriflu were local events. Across all studies of Agriflu, pain at the injection site was the most commonly reported solicited adverse reaction and was reported in 22% and 25% of subjects in the two pivotal trials. Other local solicited adverse events were reported less commonly: induration was reported in 5%-10%, swelling in 4%-6%, erythema in 5%-6%, and ecchymosis in 5%-6% of subjects in the two pivotal trials. The systemic solicited adverse reactions reported in more than 5% of subjects in either pivotal trial were headache (23%-24% of subjects), myalgia (14%-18% of subjects), malaise (12% of subjects in both studies), fatigue (9%-10% of subjects), arthralgia (5%-6% of subjects), and chills (5%-7% of subjects). The safety results of the supportive studies were similar to those of the two pivotal trials.

Information on spontaneous adverse events was reported in all studies of Agriflu. The most commonly reported spontaneous AEs included nasopharyngitis, rhinitis, and pharyngeal pain, and headache. No events of Guillain-Barré, anaphylaxis, or oculo-respiratory syndrome were reported in these studies.

In the clinical studies included in this BLA, there were a total of four deaths in subjects who received Agriflu. All deaths were in subjects 61 years of age and older; deaths were due to hypertension,, cerebral hemorrhage, acute pancreatitis, and lung adenocarcinoma. None of these deaths was judged as related to Agriflu. All of the causes of death were consistent with illnesses typically seen in elderly individuals.

The adverse events most commonly observed after vaccination with Agriflu were local events at the injection site, particularly pain. The most common systemic event was headache. No evidence for an increase in severity or seriousness of adverse events was observed by this reviewer. Therefore, the safety profile of Agriflu was acceptable for clinical approval of this application.

Finally, the applicant plans to conduct additional studies of Agriflu in children from 6 months to 17 years of age ---b(4)----------. Although pediatric studies will be deferred, as described in the Pediatric Research Equity Act, the applicant will be required to complete clinical development in the pediatric population with due diligence.

4. Significant Findings from Other Review Disciplines

4.1 Chemistry, Manufacturing and Controls (CMC)

Agriflu is a trivalent, split-virion influenza virus vaccine prepared from virus propagated in the allantoic cavity of embryonated hens' eggs. Each of the influenza virus strains is produced and purified separately. The virus is inactivated by formaldehyde and ----------b(4)----------. Antibiotics (kanamycin and neomycin sulphate), polysorbate 80, and cetyltrimethylammonium bromide are used during the manufacturing process, and trace amounts may be present in the final vaccine.

A Complete Response letter was issued on April 27, 2009 for this BLA due to concerns with the manufacturing process. Please see the CMC review. These issues have been adequately addressed by the Applicant.

4.2 Animal Pharmacology/Toxicology

The results of reproduction toxicity studies in rabbits were submitted in this BLA. Appropriate language describing the study results is included in the label. Please see Dr. Gruber's review.

5. Clinical and Regulatory Background

5.1 Disease or Health-Related Condition(s) Studied and Available Interventions

Influenza infection in the United States is characterized by seasonal epidemics, usually occurring during the winter months. During the years 1990-1999, influenza infection was responsible for an average of 36,000 deaths per year in the United States. The rates of infection are highest among children, but serious illness and death are reported more frequently among persons greater than or equal to 65 years of age and persons of any age who have chronic underlying medical conditions that place them at increased risk of complications. Influenza vaccination is the primary method for preventing influenza illness and its severe complications. In certain circumstances, antiviral medication can be an important adjunct to the vaccine for prevention and control of influenza.

The Advisory Committee on Immunization Practices (ACIP) publishes recommendations for groups of persons who should be targeted for routine administration of influenza vaccine; these include but are not limited to persons greater than or equal to 50 years of age, persons with chronic medical conditions, children aged 6 months of age and older, and health care workers.

Efficacy and effectiveness of influenza vaccine products have been evaluated in retrospective studies, prospective longitudinal studies, and challenge studies. The range of vaccine efficacy in these studies varies from 22% to 91%. In general, vaccine efficacy appears to be reduced in

adults greater than or equal to 65 years of age. In addition, immune response parameters also appear to be reduced in the elderly population.

5.2 Important Information from Pharmacologically Related Products, Including Marketed Products

Influenza vaccines have been available since the 1940s. There are currently five trivalent, inactivated, split-virion vaccines licensed in the U.S. for prevention of seasonal influenza in adults: Fluzone™, Fluarix™, Afluria™, Fluvirin™, and FluLaval™. Fluarix, Afluria and FluLaval were approved using the accelerated approval mechanism because of the shortage of influenza vaccine. Accelerated approval of these three vaccines was based on immunogenicity and safety data from studies using a surrogate marker (anti-hemagglutinin antibody response) for clinical efficacy. The clinical efficacy of Fluarix was confirmed in a clinical endpoint study, and Fluarix now has traditional approval. A live attenuated trivalent vaccine, FluMist, is also licensed in the U.S. for the prevention of influenza illness in healthy subjects 2-49 years of age.

Worldwide surveillance of influenza provides an estimate of the strains of influenza that might be in circulation in the United States. Each year, changes to the antigen content of the vaccine are made based on these surveillance mechanisms so that the vaccine might offer optimal protection from the influenza strains in circulation.

5.3 Previous Human Experience with the Product Including Foreign Experience

Agriflu was initially licensed in Italy in 1986 as Agrippal and is now licensed for use in more than 50 countries worldwide. The initial formulation of Agrippal contained thimerosal as a preservative. The formulation was changed resulting in a trace-thimerosal vaccine that was marketed starting in 2001. The applicant subsequently began producing a thimerosal-free formulation in 2003. According to the applicant, more than --b(4)--------- doses have been distributed worldwide including more than --b(4)----- doses of the thimerosal-free formulation that the applicant is proposing marketing in the U.S.

5.4 Regulatory Background Information

5.4.1. Background of Accelerated Approval Mechanism for Vaccines to Prevent Influenza

In response to a shortage of influenza vaccine available in the United States in the 2004-2005 influenza seasons, CBER developed strategies for use of the accelerated approval mechanism (21 CFR 601.40 and 21 CFR 601.41) to expedite approval of influenza vaccines in the United States. A Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting was convened on February 17, 2005 to discuss the use of the accelerated approval regulations for influenza vaccines using HI titer as surrogate endpoints that were reasonably likely to predict clinical benefit, and VRBPAC members favored the use of this approach. Guidelines for use of this mechanism were then published as FDA Guidance for Industry, “Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines.”

FDA regulations for accelerated approval state that the surrogate endpoint should be reasonably likely to predict that patients will derive clinical benefit from the study product. The surrogate marker recommended in the FDA Draft Guidance for accelerated approval of influenza vaccines is HI titers. The HI antibody assay has been widely used to measure influenza vaccine activity; in fact, the EMEA uses HI titers to measure immunogenicity in studies for yearly influenza strain change. These criteria are shown below.

Table 4: EMEA Immunogenicity Criteria for Adults for Purposes of Yearly Registration

Immunogenicity criteria	**Age group 18-60**	**Age > 60 years**
Ratio of GMT HI antibody day 21/GMT HI antibody baseline	> 2.5	> 2.0
Proportion with HI antibody titer increase 4-fold from baseline (seroconversion)	> 40%	> 30%
Proportion with HI antibody titer of at least 1:40	> 70%	> 60%

Source: Committee for Proprietary Medicinal Products (CPMP). Note for guidance on harmonisation of requirements for influenza vaccines. CPMP/BWP/214/96. The European Agency for the Evaluation of Medicinal Products (EMEA), March 1997.

The criteria recommended by CBER for evaluation of HAI endpoints for studies of influenza vaccine using surrogate markers are loosely based on these EMEA criteria for yearly strain change. The criteria were modified for approval of a new influenza vaccine and are described in detail in the Guidance. Modifications include:

- The use of 2 endpoints in the evaluation of a new vaccine: 1) seroconversion defined as a four-fold or greater rise in HI antibody titers over baseline for all three vaccine antigens and 2) the proportion of subjects with an HI antibody titer of at least 1:40 following vaccination for each of the three vaccine antigens.
- The lower bounds of the 95% confidence intervals, not the point estimates, are required to be above the target goal.
- All six endpoints are required to be achieved, i.e. two endpoints for each of the three vaccine antigens.

These endpoints were discussed with the Applicant and agreed upon prior to the submission of the licensing application.

The regulations for accelerated approval specify that applicants are required to conduct adequate and well-controlled confirmatory studies. The Applicant was informed that the accelerated approval mechanism using surrogate endpoints rests upon the commitment to conduct clinical studies to confirm the surrogate endpoint. The Applicant has recently conducted a Phase III study using clinical endpoints; at the time of BLA filing, the study results were still being analyzed.

Finally, this regulatory pathway of accelerated approval for influenza vaccines is dependent on a well-characterized projected seasonal shortage of inactivated trivalent influenza vaccine at the time of approval. The Centers for Disease Control have declared that a seasonal influenza vaccine shortage currently exists in the United States.

5.4.2 Regulatory Background Regarding Agriflu

Novartis first submitted an IND (-b(4)---) for Agriflu on February 20, 2007. The original IND submission contained the protocol for Study V71P5; the results of this study provide the majority of data to support the safety and immunogenicity of Agriflu. The other studies included in this BLA had been completed at that time.

An internal meeting to discuss the submission of a BLA to support licensing of Agriflu in the U.S. was held on February 19, 2008. A Type B, pre-BLA meeting between CBER and the applicant was held on February 26, 2008. An additional Type C meeting to discuss manufacturing issues was held on May 23, 2008.

A Complete Response letter was issued for this BLA on April 27, 2009 because of chemistry and manufacturing concerns. The Applicant submitted a reply to the Complete Response letter on May 29, 2009, in which these concerns were adequately addressed.

6 Clinical Data Sources, Review Strategy and Data Integrity

6.1 Material Reviewed

This BLA was submitted electronically. The clinical sections, labeling, and financial information were reviewed. This included the Clinical Study Reports, the pertinent Case Report Tabulations, and Case Report Forms.

6.1.1 BLA Volume Numbers Which Serve as a Basis for the Clinical Review

The supplement contained 12 Items. The following Items were reviewed by this reviewer: Item 1 Table of Contents, Item 2 Labeling, Item 3 Summary, Item 8 Clinical, Item 11 Case Report Tabulations, Item 12 Case Report Forms, and Item 19 Financial Information.

6.2 Tables of Clinical Studies

The number of subjects listed in the tables below represents the total number of subjects enrolled in the studies, not the number of subjects receiving Agriflu.

Table 5: Pivotal Studies for Support of Agriflu Immunogenicity and Safety

Study	Type	Control	Total # Subjects	Age	Country
V71P5	Phase III, randomized, observer-blind, immunogenicity and safety study	Fluvirin	1893	3-64 years	Argentina
V71P6	Phase III, randomized, observer-blind, immunogenicity, safety, and lot-to-lot consistency study	Fluvirin	1507	18-49 years	Dominican Republic

Source: BLA 125297, Section 2.7.6 pages 1-2.

The results of the following studies were submitted to demonstrate Agriflu immunogenicity. These three trials were designed to study the immunogenicity and safety of a cell-derived seasonal influenza vaccine. Agriflu was the active control in each study.

Table 6: Supportive Studies for Immunogenicity

Study	Type	# Subjects	Age	Country
V58P2	Phase II, randomized, observer-blind immunogenicity and safety study	223	≥ 18 yrs	New Zealand
V58P4	Phase III, blind, randomized, non-inferior	2654	≥ 18 yrs	Poland
V58P9	Phase III, lot-to-lot consistency, randomized	1200	18-60 yrs	Lithuania

Source: BLA 125297, Section 2.7.6 pages 1-2.

Table 7: Supportive Studies for Safety

Study	Type	# Subjects	Age	Country
V64P1	Phase II, observer-blind, randomized of thimerosal reduced compared to Agriflu containing thimerosal	295	≥ 18 yrs	Italy
V71P1	Phase II, observer-blind, randomized of thimerosal-reduced compared to thimerosal-free Agriflu	295	≥ 18 yrs	Italy
V71P2	Phase II, observer-blind, randomized of thimerosal-reduced compared to thimerosal-free Agriflu	498	3-64 yrs	Italy
V71P3	Phase II, single arm, open-label study of thimerosal-free formulation	130	≥ 18 yrs	Lithuania
V64P1S	Seasonal Registrational Trial (2002-03)	147	≥ 18 yrs	Italy
V71P1S	Seasonal Registrational Trial (2003-04)	112	≥ 18 yrs	Italy
V71P2S	Seasonal Registrational Trial (2004-05)	119	≥ 18 yrs	Italy
V71P3S	Seasonal Registrational Trial (2005-06)	111	≥ 18 yrs	Italy
V71P4S	Seasonal Registrational Trial (2006-07)	124	≥ 18 yrs	Italy
V58P4E1	One Year Follow-up study of subjects in V58P4	2235	≥ 18 yrs	Lithuania

Source: BLA 125297, Section 2.7.6 pages 1-2.

6.3 Good Clinical Practices (GCP) and Data Integrity

According to the applicant, the studies submitted in support of the immunogenicity and safety of Agriflu were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practices for both the country in which the study was performed and the International Conference on Harmonisation guidelines.

Investigators from BIMO inspected the two study sites for Study V71P6. Both sites were in Santo Domingo, Republica Dominicana. The BIMO investigator reported that the components of the physical examinations for eligibility varied and were not always as described in the study protocol. For example, some subjects had abdominal examinations while sitting in a chair, and investigators did not have an otoscope. In addition, temperature was not monitored at the second study visit, and blood pressure was inconsistently monitored. BIMO also noted that 51 subjects were enrolled at a third study site in Santo Domingo, which was not listed in Form FDA 1572. FDA 483 warning letters were issued to both study sites. However, the BIMO investigator did note that there was no evidence of underreporting of adverse events. These issues did not affect the immunogenicity results from Study V71P6, and there are sufficient safety data from other studies included in this BLA to analyze the safety of Agriflu in spite of irregularities at these two study sites.

6.4 Financial Disclosures

The applicant requested financial disclosure information from all principal investigators. A total of 92.5% of investigators responded to this request; of the eight investigators who did not respond, none were involved in the two pivotal clinical trials. No clinical investigators were or are full or part-time employees of Novartis Vaccines and Diagnostics. No disclosable financial information was reported by any of the clinical investigators who provided financial disclosure information. FDA Form 3454 was included in the BLA submission.

7 Human Pharmacology

No human pharmacology data were submitted in this application.

8 Clinical Studies

8.1 Trial #1 - Study V71P5:

A phase 3, observer-blind, randomized, controlled, multicenter study to evaluate safety, tolerability, and immunogenicity of two trivalent subunit inactivated influenza vaccines (Agriflu and Fluvirin) in healthy children aged 3 to 8 years, in healthy children / adolescents aged 9 to 17 years and in healthy adults aged 18 to 64 years

8.1.1 Objective/Rationale

The primary objective was to evaluate immunogenicity, measured by percentage of subjects achieving a HI titer $\geq$ 1:40 and by percentage of subjects achieving seroconversion [defined as negative pre-vaccination serum with post-vaccination serum $\geq$ 1:40 or significant increase (defined as a four fold or more increase in HI titer from non-negative pre-vaccination serum)] in healthy adults aged 18 to 64 years after one injection of Agriflu.

The secondary objectives were to descriptively evaluate immunogenicity of:

- One injection of Fluvirin administered to healthy adults aged 18 to 64 years of age,
- One injection of either Agriflu or Fluvirin administered to healthy children / adolescents aged 9 to 17 years of age, and
- Two injections of either Agriflu or Fluvirin administered 4 weeks apart to healthy children aged 3 to 8 years of age.

The safety objectives were to evaluate the safety and tolerability of:

- Two injections of either Agriflu or Fluvirin, administered 4 weeks apart to children aged 3 to 8 years, and
- One injection of either Agriflu or Fluvirin, administered to children / adolescents aged 9 to 17 years and adults aged 18 to 64 years.

According to the study protocol, the purpose of the control arm, Fluvirin, was primarily to provide a comparative assessment for safety, not immunogenicity.

8.1.2 Design Overview

Study V71P5 was a Phase III, randomized, observer-blind, controlled study of Agriflu compared to Fluvirin in 1893 healthy subjects from 3 to 64 years of age. Subjects were stratified by age group (3-8 years, 9-17 years, and 18-64 years) then randomized in 2:1 ratio to Agriflu or Fluvirin. The study was to enroll 1800 subjects: 600 children 3-8 years of age, 600 children 9-17 years of age, and 600 adults.

The trial was observer-blind. Designated study personnel were responsible for administering the study vaccines and were instructed not to reveal the identity of the study vaccines to the subject or to the investigative site personnel involved in the monitoring or conduct of the trial. These designated personnel were not to have any contact with the subjects after the administration of the study vaccine.

Subjects 3 to 8 years of age were to receive two 0.5 mL intramuscular doses of study vaccine with 4 weeks between doses; subjects 9 years of age and older were to receive a single, 0.5 mL intramuscular dose of study vaccine.

Subjects were screened, enrolled, and vaccinated on Day 1 of the study. At that visit, all subjects had a medical history obtained and a physical examination; entry criteria were reviewed for each subject prior to enrollment.

There were three study visits for subjects 3 to 8 years of age, at Days 1, 29, and 50; parents / guardians of these subjects were contacted by telephone for follow-up at Day 209. Subjects 9 years of age and older had two clinic visits at Days 1 and 22, and either subjects or parents / guardians were contacted by telephone at Day 181 for safety follow-up.

8.1.3 Population

The study enrolled subjects who were in good health as determined by medical history, physical examination, and clinical judgment of the Investigator.

Reasons for study exclusion included laboratory-confirmed influenza disease within 6 months of enrollment; receipt of another vaccine within 30 days of enrollment; history of anaphylaxis or serious vaccine reactions; allergy to eggs, egg products, or any other vaccine component; known of suspected impairment of immune function; any disease or infection requiring systemic antibiotic or antiviral therapy in previous 30 days; and any serious disease. Subjects aged 3 to 8 years of age who had previously received an influenza vaccination were excluded from study participation.

Subjects could be removed from study participation due to withdrawing consent, non-compliance, febrile convulsions and neurological disturbances after vaccination, hypersensitivity

reaction after vaccination, or other adverse events post-vaccination that might compromise the subject's well being.

> *Reviewer comment*: The withdrawal criteria primarily affected the children aged 3 to 8 years of age. These children were to have two vaccinations and could be withdrawn after a single vaccination. All other subjects were to get one vaccination and withdraw criteria would not change their study treatment.

All female subjects of child bearing potential were queried by study staff to determine the date of the last menstrual period. Females of child bearing potential were required to have a negative urine pregnancy test prior to vaccination. Any subject who became pregnant during the trial was followed to obtain pregnancy outcome.

8.1.4 Products mandated by the protocol

Agriflu was supplied as 0.5 mL dose in pre-filled syringes. Each 0.5 mL vaccine contained the purified viral envelope-glycoproteins, neuraminidase (NA) and hemagglutinin (HA) derived from three strains [including 15 μg of HA for each of the strains A/New Caledonia/20/99 (H1N1)-like, A/Wisconsin/67/2005 (H3N2)-like, and B/Malaysia/2506/2004-like] recommended for the 2007 influenza season in the Southern Hemisphere. The lot number was 060103A and expiry date was June 2007.

Fluvirin was supplied as multiple dose vials containing the purified viral envelope-glycoproteins, NA and HA derived from three strains [including 15 μg of HA for each of the strains A/New Caledonia/20/99 (H1N1)-like, A/Wisconsin/67/2005 (H3N2)-like, and B/Malaysia/2506/2004-like] recommended for the 2007 influenza season in the Southern Hemisphere; lot number: 73196 and expiry date June 2007. The multi-dose vials contained thiomersal as a preservative; there was 24.5 μg mercury per dose of Fluvirin.

Vaccination was two 0.5 mL doses administered 4 weeks apart for children 3 to 8 years of age and one 0.5 mL dose for subjects 9 years of age and older. All injections were administered intramuscularly in the deltoid muscle, preferably of the non-dominant arm.

8.1.5 Endpoints

The variable to measure immunogenicity was the strain-specific anti-hemagglutinin antibody titer. HI antibody levels were measured at baseline and on Days 29 and 50 post vaccination for children 3-8 years, and on Day 22 post-vaccination for subjects 9 years of age and older.

The endpoints used for evaluation of immunogenicity were point estimates and 95% confidence intervals for geometric mean antibody titers, geometric mean ratios, seroconversion rate (pre-vaccination titer <10 with post-vaccination titer $\geq$ 1:40), significant increase in seroconversion rate *(*defined as a $\geq$ 4 fold increase from baseline titer $\geq$ 10); and the percentage of subjects with post-vaccination titer $\geq$ 1:40.

Anti-HI assays were performed at the Novartis laboratory in --b(4)----------.

8.1.6 Safety Monitoring

All subjects were monitored in the study clinic for 30 minutes post-vaccination. Diary cards were dispensed post-vaccination. Subjects and/or their parents / guardians were instructed to complete diary cards to record solicited reactions, axillary temperature, use of analgesics or antipyretics, impact on daily activities (e.g., stayed at home due to an adverse reaction), and other adverse events. Subjects were to record information in the diaries starting six hours post-vaccination and ending seven days post-vaccination. Diary cards were reviewed at each study visit and were collected on Day 50 for subjects 3 to 8 years of age and on Day 22 for subjects 9 years of age and older. Data from diary cards were transcribed to the relevant area of the case report forms.

Information on solicited adverse reactions was collected for 7 days post-vaccination (day of vaccination and next 6 days). Information was solicited for both local reactions (ecchymosis, erythema, induration, swelling, and pain) and for general reactions (chills, malaise, myalgia, arthralgia, headache, sweating, fatigue, and body temperature). The severity of local adverse reactions were categorized as none, 1 to $\leq$ 10 mm, 11 to $\leq$ 25 mm, 26 to $\leq$ 50 mm, 51 to $\leq$ 100 mm, and > 100 mm (severe). Axillary body temperature was categorized as < 38º C and $\geq$ 38º C. Other adverse events will be categorized as mild if the AE is transient and does not limit daily activity, moderate if there is some limitation of normal daily activity, and severe if the subject is unable to perform normal daily activities.

Information on unsolicited adverse events was collected for 21 days post-vaccination for subjects 9 years of age and older and for the 29 days post-vaccination in children 3-8 years. Information on serious adverse events, medically significant events, and adverse events leading to study discontinuation were collected for entire study period (6 months after last vaccination). Information on concomitant medication use was collected for 21 days (subjects 9 years of age and older) or 29 days (subjects 3 to 8 years of age) post-vaccination for prescription medications. Information on non-prescription medication use was collected for 7 days post-vaccination; this included any use of analgesics or antipyretics. Information on adverse events occurring after the last study visit was collected by telephone contact six months after the last study vaccination.

> *Reviewer comment*: Medically significant events were followed throughout the entire 6 month study period. The definition of medically significant events could not be found in the study protocol or Clinical Study Report. The Applicant does state that one example of a medically significant event was new onset chronic disease.

8.1.7 Statistical considerations

The criteria for demonstration of immunogenicity from FDA Guidance for Industry, “Clinical

Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines" were used to assess Agriflu immunogenicity in adults 18 to 49 years of age. Immunogenicity was demonstrated if:

- the lower limit of the 95% confidence interval (CI) for the percentage of subjects with seroconversion or significant increase in HI antibody titer meets or exceeds 40%
- the lower limit of the 95% CI for the percentage of subjects achieving an HI antibody titer ≥40 meets or exceeds 70%.

For the primary immunogenicity objective, with 360 evaluable subjects in each age group, the lower limits of the 95% CI around the estimated percentage of subjects achieving an HI titer ≥40 or with seroconversion would meet or exceed the threshold level of 70% and 40% respectively, if the percentage of subjects with post-vaccination HI titers ≥ 1:40 was at least 75% (95% CI: 70.2% - 79.4%), and the percentage of subjects with seroconversion or significant increase was at least 46% (95% CI: 40.8% - 51.3%).

The analysis of immunogenicity in the pediatric age group was descriptive and included the use of Geometric mean ratio (GMR). GMR was defined as the ratio of the post-vaccination HAI titer value to antibody titer on study Day 1.

The time points for measurement of immunogenicity were Day 50 for subjects 3 to 8 years of age and Day 22 for subjects 9 years of age and older.

Study populations were as listed below.

- All randomized population was used for demography and subject listings.
- Full Analysis Set / Modified Intention-to-Treat (MITT) population, Immunogenicity included all randomized subjects in the enrolled population who received a study vaccination and provided at least one evaluable serum sample.
- Per protocol (PP) population, Immunogenicity included all subjects in the Full Analysis Set/MITT population who received all the relevant doses of vaccine correctly, provided evaluable serum samples at the relevant time points, and had no major protocol violations. A major protocol violation was defined as a protocol deviation that was considered to have a significant impact on the immunogenicity results of the subject.
- Exposed population included all enrolled subjects who received a study vaccination.
- The safety population included all subjects in the Exposed population who provided post-baseline safety data.

8.1.8 Results

Study V71P5 was conducted at two study sites in Argentina. The study vaccines included strains recommended for the 2007 influenza season in the Southern Hemisphere. The first subject was enrolled on April 11, 2007 and the last subject completed the study on December 20, 2007.

8.1.8.1 Populations enrolled/analyzed

A total of 1893 subjects were enrolled in Study V71P5: 1262 in the Agriflu arm and 631 in the Fluvirin arm. Of these subjects, 601 were from 3 to 8 years of age, 600 were from 9 to 17 years of age, and 692 were adults from 18 to 64 years of age. Subject disposition is shown in the table below.

Table 8: Study V71P5 – Subject Disposition

	3-8 Years		**9-17 Years**		**18-64 Years**	
	Agriflu	**Fluvirin**	**Agriflu**	**Fluvirin**	**Agriflu**	**Fluvirin**
Enrolled / Safety Population	402	199	400	200	460	232
Completed study	392 (98%)	195 (98%)	400 (100%)	199 (100%)	435 (95%)	222 (96%)
Premature discontinuation	10	4	0	1	25	10
Consent withdrawn	9	4	0	1	0	0
Lost to F/U	1	0	0	0	25	10

Source: BLA 125297, CSR, Table 10.1-1, page 54

As shown in the table above, the majority of subjects (97%) completed the study. The percentage of subjects prematurely discontinuing the study was low and similar in the two treatment arms. The main reason for premature discontinuation was loss to follow-up.

Subjects were excluded from the Per Protocol analysis population for immunogenicity because of major protocol deviations. The types of major protocol violations are shown in the table below.

Table 9: Study V71P5 – Subject Disposition

	3-8 Years		9-17 Years		18-64 Years	
	Agriflu	**Fluvirin**	**Agriflu**	**Fluvirin**	**Agriflu**	**Fluvirin**
Enrolled / Safety Population	402	199	400	200	460	232
Per Protocol Population	296 (74%)	149 (75%)	393 (98%)	192 (96%)	424 (92%)	219 (94%)
Reasons for Exclusion						
Blood draw outside window	8	4	1	0	20	9
No 2nd blood draw	10	4	0	1	14	3
Entry criteria violation					0	1
Received excluded medication	4	0	1	1	2	1
Age outside of cohort	2	0	0	1	2	0
Received wrong vaccine	0	0	3	3	0	0
Received non-study vaccine	0	0	2	2	0	0
No Visit 2 or 3	10	4	--	--	--	--
No 2nd vaccination	6	3	--	--	--	--

Source: BLA 125297, CSR, pages 58-62

Reviewer comment: As shown in the table above, the Per Protocol population was the Enrolled population minus the number of subjects with major protocol violations. The number of protocol violations and reasons for exclusions do not equal the number of subjects who were excluded, because some subjects had more than one major protocol violation.

A total of 142 subjects were enrolled at site 14. Immunogenicity results of 137 of the site 14 subjects, all from 3 to 8 years of age, were excluded from the evaluation of immunogenicity. The antibody titers for these subjects were lower after the first vaccination than at baseline. The reason for the difference in antibody titers is not known; the Applicant states that it was not due to mislabeling since bar code labels used on serum samples matched those for visit and subject number. According to the Applicant, an internal audit is underway. The Per Protocol analysis of immunogenicity in this age group excludes all subjects from site 14.

Reviewer comment: As a result of excluding subjects from this site, one-fourth of enrolled subjects 3 to 8 years of age were not included in the Per Protocol analysis. This is a large percentage of subjects and may have affected the study outcome in this age stratum. In addition, it raises concerns about the study conduct, particularly at sites

enrolling children. However, the study results for V71P5 are being used to support use of Agriflu in adults and not in children.

Demographics

Subject demographics are shown in the following table.

Table 10: Study V71P5 – Demographic Characteristics of Study Population

	3-8 Years N=692		**9-17 Years N=600**		**18-64 Years N=601**	
	Agriflu	**Fluvirin**	**Agriflu**	**Fluvirin**	**Agriflu**	**Fluvirin**
Mean Age	5.5	5.5	12.7	12.8	38.8	37.8
% Female	43%	49%	56%	55%	64%	56%
Race						
%White	100%	100%	100%	100%	80%	78%
%Hispanic	0	0	0	0	20%	22%
%Asian	0	0	0	0	<1%	0
Previous Flu Vaccination	N/A	N/A	2%	2%	22%	21%

Source: BLA 125297, CSR, Table 11.2-1, page 63

Baseline characteristics were similar between the two study arms. All pediatric subjects were Caucasian, while 79% of adult subjects were Caucasian and 20.5% were Hispanic. Previous influenza vaccination was an exclusion criterion for subjects 3 to 8 years of age, was rare in the 9 to 17 year old group and uncommon in adults (22%).

Reviewer comment: Baseline characteristics were similar between study arms. The racial and ethnic make up of the study population was primarily Caucasian and does not represent a more diverse U.S. population.

8.1.8.2 Immunogenicity endpoints/outcomes

The primary objective was to evaluate immunogenicity as measured by 1) the percentage of subjects achieving a post-vaccination HI titer of 1:40 or greater and by 2) percentage of subjects achieving seroconversion (defined as negative pre-vaccination serum / post-vaccination serum ≥ 1:40 or significant increase (defined as a four fold or more increase in HI titer from non-negative pre-vaccination serum) in healthy adults aged 18 to 64 years. The criteria for successfully meeting this objective were:

- a lower bound of the two-sided 95% confidence interval of subjects with post-vaccination HI titers ≥ 1:40 of 70% or higher, and
- a lower bound of the two-sided 95% confidence interval for seroconversion or for subjects with a significant increase in HI titer of 40% or more.

As shown in the table below, the baseline HI titers were similar between the treatment arms for each of the three vaccine strains. In addition, the percentage with a baseline titer of 1:40 or greater was similar between the two study arms.

Table 11: Study V71P5 – Baseline HI Antibody Levels and Percentage of Subjects with HI Titers ≥ 1:40 at Baseline

	Agriflu			Fluvirin		
	A/H1N1	**A/H3N2**	**B**	**A/H1N1**	**A/H3N2**	**B**
Baseline GMT	20	22	11	18	22	10
% of Subjects with HI≥1:40 at Baseline	38%	40%	18%	35%	42%	18%

Source: BLA 125297, CSR, Table 11.4.1.1-1, page 66

The results for the primary endpoint are shown below.

Table 12: Study V71P5 – Percentage of Subjects 18 to 64 Years of Age with Seroconversion or with HI Titers ≥ 1:40 Post-Vaccination

	Agriflu N=424			Fluvirin N=219		
	A/H1N1	**A/H3N2**	**B**	**A/H1N1**	**A/H3N2**	**B**
Seroconversion Rate	74%	72%	77%	86%	89%	74%
LL 95%CI	69%	68%	72%	81%	84%	68%
% of Subjects with HI≥1:40 Post-Vaccination	93%	96%	91%	99%	100%	86%
LL 95%CI	90%	94%	87%	97%	98%	81%

Source: BLA 125297, CSR, Table 11.4.1.1-1, page 66

Both Agriflu and Fluvirin met the criteria outlined in the FDA Guidance for Industry, "Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines" for all three strains. Specifically, the lower bound of the 95% confidence interval for seroconversion was greater than 40% for all three strains and the percentage of subjects with HI titers of 1:40 or higher post-vaccination was greater than 70% for all three strains.

> *Reviewer comment*: The study results met the criteria for demonstration of immunogenicity in adults from 18 to 64 years of age as outlined in the study protocol.

Secondary immunogenicity objectives

The secondary objectives included the evaluation of the immunogenicity of Fluvirin. As discussed above, the percentage of subjects with seroconversion and with post-vaccination titers ≥ 1:40 after vaccination with Fluvirin was higher than the target criteria outlined in the FDA Guidance for Industry.

Other secondary endpoints were the post-vaccination geometric mean titer and the geometric mean ration between pre- and post-vaccination HI titers. These are shown in the table below.

Table 13: Study V71P5 - Post-Vaccination Geometric Mean Titers and Geometric Mean Ratios for HI Antibodies in Subjects 18 to 64 Years of Age

	Agriflu	Fluvirin

	N=424			N=219		
	A/H1N1	**A/H3N2**	**B**	**A/H1N1**	**A/H3N2**	**B**
Baseline GMT	20	22	11	18	22	10
Post-Vaccination GMT	244	219	126	512	485	104
LL 95%CI	214	196	113	426	415	90
GMR	12	9.9	12	28	22	10
LL 95%CI	10	8.6	10	23	18	8.4

Source: BLA 125297, CSR, Table 11.4.1.1-1, page 66

Reviewer comment: The post-vaccination titers were substantially higher than pre-vaccination titers for subjects in both vaccine arms. Increases in antibody titer were higher in the Fluvirin arm, particularly antibody titers to the influenza A strains. The difference in titers from baseline to Day 21 was 8.4 fold higher or more. Again, this increase was greater in the Fluvirin arm for the influenza A strains. The GMR for antibodies to the A/H1N1 strain were 23 fold higher than baseline in the Fluvirin arm and 10 fold higher in the Agriflu arm; the difference between arms was less marked for the A/H3N2 strain (18 fold increase in the Fluvirin arm and 8.6 fold increase in the Agriflu arm). Finally, the GMR for the influenza B strain was slightly higher in Agriflu recipients (10 fold) than in Fluvirin recipients (8.4 fold).

Immunogenicity results for pediatric subjects

The primary endpoint for immunogenicity in adults was seroconversion and percentage of subjects with post-vaccination HI titers of 1:40 or greater. The immunogenicity results for the pediatric patients were secondary endpoints, and the analyses of these results were pre-defined as "descriptive." The percentage of pediatric subjects from 3 to 8 years of age who seroconverted post-vaccination or had post-vaccination HI titers of 1:40 or higher is shown in the table below.

Table 14: Study V71P5 – Percentage of Pediatric Subjects from 3 to 8 Years of age with Seroconversion or with HI Titers ≥ 1:40 Post-Vaccination (Per Protocol Population)

	Agriflu			Fluvirin		
	A/H1N1	**A/H3N2**	**B**	**A/H1N1**	**A/H3N2**	**B**
Seroconversion Rate	95%	86%	83%	97%	95%	79%
LL 95%CI	91%	82%	78%	92%	90%	72%
% of Subjects with HI ≥1:40 Post-Vaccination	97%	100%	85%	99%	99%	81%
LL 95%CI	94%	99%	80%	95%	96%	73%

Source: BLA 125297, CSR, Table 11.4.1.2.3-1, page 72

Although the study was not designed to use FDA criteria for demonstration of immunogenicity in pediatric patients, the results for subjects 3 to 8 years of age met the criteria for adults as described in the FDA Guidance for Industry for all three strains and for both seroconversion and for percentage of subjects with post-vaccination HI titers of 1:40 or higher.

Reviewer comment: As shown in the table above, the percentage of subjects from 3 to 8 years of age with seroconversion or with post-vaccination HI titers of 1:40 or higher was slightly lower when the subjects from the one study site were included. This study site enrolled approximately one-fourth of all subjects 3 to 8 years of age. Although there is

little difference between the results with and without this site, it does not alleviate this reviewer's concern about the study conduct as regards the youngest age cohort. No sites from this study were inspected by FDA.

Immunogenicity results for children from 9 to 17 years of age are shown in the table below.

Table 15: Study V71P5 – Percentage of Pediatric Subjects from 9 to 17 Years of age with Seroconversion or with HI Titers ≥ 1:40 Post-Vaccination (Per Protocol Population)

	Agriflu			**Fluvirin**		
	A/H1N1	**A/H3N2**	**B**	**A/H1N1**	**A/H3N2**	**B**
Seroconversion Rate	92%	67%	81%	91%	92%	73%
LL 95%CI	88%	62%	76%	86%	87%	67%
% of Subjects with HI ≥1:40 Post-Vaccination	99%	100%	93%	98%	100%	89%
LL 95%CI	97%	99%	90%	96%	98%	84%

Source: BLA 125297, CSR, Table 11.4.1.2.2-1, page 69

As shown in the table above, the percentage of subjects from 9 to 17 years of age with seroconversion and the percentage with a post-vaccination titer of 1:40 or higher met the goals for demonstration of immunogenicity as outlined in the FDA Guidance for Industry.

Reviewer comment: The immunogenicity results were similar for Agriflu and for Fluvirin except for the seroconversion rate to the A/H3N2 strain and the influenza B strain. The seroconversion rate for influenza A/H3N2 was higher in the Fluvirin arm (+25%), while the seroconversion rate for influenza B was higher in the Agriflu arm (+9%). Because the majority of subjects in both arms had post-vaccination titers of 1:40 or greater, the clinical relevance of this finding is unknown.

Subgroup analyses

Subgroup analyses were performed for all three age groups. Because the Applicant is pursuing an indication for adults only, the subgroup analyses for adults, and not children, are presented in this review. Percentage of adult subjects with HI titers ≥ 1:40 post-vaccination by vaccination history is shown in the table below.

Table 16: Study V71P5 – Percentage of Subjects 18 to 64 Years of Age with Post-Vaccination HI Titers ≥ 1:40 by Previous Influenza Vaccine History

Influenza Strain	Timing	Agriflu			Fluvirin		
		+ Hx*	Neg Hx*	Unknown	+ Hx*	Neg Hx*	Unknown
A/H1N1	**Pre**	61%	30%	47%	68%	26%	25%
	Post	93%	93%	94%	98%	99%	100%
A/H3N2	**Pre**	55%	37%	24%	66%	36%	25%
	Post	96%	96%	100%	100%	100%	100%
B	**Pre**	35%	13%	18%	47%	10%	25%
	Post	81%	94%	82%	87%	86%	88%

* + Hx is positive history of influenza vaccination, Neg Hx is no history of influenza vaccination
Source: BLA 125297, CSR, Table 11.4.2.1.2.3, pages 291-305

Reviewer comment: As shown in the table above, the percentage of adult subjects with HI titers of 40 or greater post-vaccination was similar for the influenza A strains regardless of vaccine history. This may have been due to the high percentage of subjects with HI titers ≥ 1:40 at baseline, which left little room for any increase in antibody titer post-vaccination. The percentage of subjects with HI titers ≥ 1:40 was lower at baseline and post-vaccination for influenza B. Post-vaccination titers were similar regardless of vaccine history. In addition, results were similar in both the Agriflu and Fluvirin arms.

Results by gender are shown in the table below.

Table 17: Study V71P5 – Point Estimates for Immunogenicity Results by Gender (Per Protocol Population of Subjects from 18 to 64 Years of Age)

Influenza Strain	Timing*	Agriflu		Fluvirin	
		Female	Male	Female	Male
Seroconversion Rate					
A/H1N1	**Post**	75%	71%	83%	89%
A/H3N2	**Post**	74%	70%	88%	90%
B	**Post**	76%	78%	71%	79%
Percentage of Subjects with Post-Vaccination HI Titers ≥ 1:40					
A/H1N1	**Pre**	35%	43%	33%	36%
	Post	94%	91%	98%	100%
A/H3N2	**Pre**	39%	42%	41%	43%
	Post	95%	98%	100%	100%
B	**Pre**	16%	22%	20%	16%
	Post	89%	93%	83%	90%

*Timing is Pre- or Post-Vaccination
Source: BLA 125297, CSR, Table 11.4.2.1.2.5, pages 319-332 and Amendment 016, table 18b-1, page 52.

Reviewer comment: The results for adult males and females were similar. The results were also similar in both the Agriflu and Fluvirin groups.

The Applicant also provided immunogenicity results by age strata in the adult population. These results are shown below.

Table 18: Study V71P5 – Point Estimates for Immunogenicity Results by Age (Per Protocol Population)

Influenza Strain	Agriflu		Fluvirin	
	18-49 Years N=320	50-64 Years N=104	18-49 Years N=168	50-64 Years N=51
Seroconversion Rate				
A/H1N1	77%	63%	90%	73%
A/H3N2	73%	71%	90%	84%
B	81%	63%	79%	59%
Percentage of Subjects with Post-Vaccination HI Titers ≥ 1:40				
A/H1N1	95%	87%	100%	96%
A/H3N2	97%	94%	100%	100%
B	96%	74%	90%	75%

Source: Amendment 016, table 18c-1, page 54.

Reviewer comment: As shown in the table above, the seroconversion rates in subjects from 50 to 64 years of age were substantially lower than in subjects from 18 to 49 years of age. This was observed in both treatment arms. The percentage of subjects with post-vaccination HI titers of 1:40 or greater was similar in the two age groups for both influenza A strains but was lower in the older age group for the influenza B strain. Although it is known that antibody response to influenza vaccines decreases with age, it is unclear at what age and at what antibody level these decreases become clinically meaningful. In addition, the results for Agriflu were similar to those for the licensed comparator.

8.1.8.3 Safety outcomes

Solicited adverse events

Information on solicited adverse reactions (local and general) was collected for 7 days post-vaccination (day of vaccination and next 6 days). Information on unsolicited adverse events was collected for 21 days post-vaccination for subjects 9 years of age and older and for the 29 days post-vaccination in children 3-8 years. Information on serious adverse events, new onset chronic illness, and adverse events leading to study discontinuation were collected for the entire study period (6 months after last vaccination).

The overall percentage of subjects with different types of solicited adverse events is presented by age in the table below.

Table 19: Study V71P5 – Percentage of Subjects with Solicited Adverse Events by Age

	3-8 Years of Age				9-17 Years of Age		18-64 Years of Age	
	1st vaccination		2nd vaccination					
	Agriflu	**Fluvirin**	**Agriflu**	**Fluvirin**	**Agriflu**	**Fluvirin**	**Agriflu**	**Fluvirin**
Any	32%	37%	22%	23%	42%	41%	50%	55%
Local	23%	28%	17%	20%	34%	31%	35%	38%
Systemic	16%	19%	10%	11%	23%	25%	32%	36%
Other	9%	7%	8%	4%	3%	5%	7%	7%

Source: BLA 125297, CSR, Tables 12.2.1-1 and 12.2.1-2, pages 80-81

Overall, the percentages of subjects with solicited adverse events were similar between the two vaccine arms when compared by subject age.

> *Reviewer comment*: The percentage of subjects with any solicited AE increased with increasing age cohort; solicited AEs were reported in approximately one-third of subjects 3 to 8 years of age and in approximately one-half of adult subjects. This increase was largely due to an increase in general solicited AEs. The reason for this increase is unclear but may be related to a young child's inability to articulate symptoms such as myalgia, arthralgia, fatigue, etc.

In subjects 3 to 8 years of age, solicited adverse events were less common after the first vaccination than after the second.

"Other" solicited AEs include percentage of subjects with analgesics/antipyretics use and percentage that stayed home due to a solicited adverse event. This result was similar in the 3 to 8 year age group and in adults, and the percentage of subjects with analgesic/antipyretic use or who stayed home was slightly lower in the 9 to 17 year age group.

The individual types of solicited adverse events are shown in the tables below. Grade 3 AEs for induration, swelling, erythema, and ecchymosis are not included in the table below because there were no Grade 3 AEs for these solicited events. The results for subjects 3 to 8 years of age are displayed separately because of the need for two vaccinations in that age group.

Table 20: Study V71P5 – Percentage of Subjects with Individual Local Solicited Adverse Events (Subjects 9-17 and 18-64 Years of Age)

		9-17 Years of Age		18-64 Years of Age	
		Agriflu	**Fluvirin**	**Agriflu**	**Fluvirin**
Pain	**Any**	29%	29%	25%	30%
	Severe	1%	0	<1%	0
Induration	**Any**	7%	7%	8%	10%
Swelling	**Any**	7%	7%	6%	6%
Erythema	**Any**	2%	2%	6%	5%
Ecchymosis	**Any**	2%	1%	5%	6%

Source: BLA 125297, CSR, Table 12.2.3-1, page 86

The most commonly reported local solicited AE in all age groups was pain. Grade 3 local AEs were only observed with pain, and were extremely uncommon. According to the Applicant,

local solicited adverse events were transient; and 1% of subjects or less had local solicited AEs present on Day 7.

> *Reviewer comment*: The frequency of local solicited events in subjects 9 years of age and older was similar in the two arms for each of the two vaccines. The frequency of local solicited AEs was 10% or lower for all individual AEs except pain. Grade 3 events were only observed for pain and were reported uncommonly.

Solicited local adverse events for children 3 to 8 years of age are shown in the table below.

Table 21: Study V71P5 – Percentage of Subjects with Individual Local Solicited Adverse Events (Subjects 3-8 Years of Age)

		After 1st Vaccination		**After 2nd Vaccination**	
		Agriflu	**Fluvirin**	**Agriflu**	**Fluvirin**
Pain	**Any**	17%	20%	14%	18%
	Severe	1%	1%	0	1%
Swelling	**Any**	5%	8%	3%	4%
Induration	**Any**	3%	5%	3%	4%
Ecchymosis	**Any**	4%	5%	3%	3%
Erythema	**Any**	2%	3%	1%	2%

Source: BLA 125297, CSR, Table 12.2.3-2, page 87

As in older subjects, the most commonly reported local solicited adverse event in subjects 3 to 8 years of age was pain. The frequency of each local adverse event was slightly lower after the second vaccination. The majority of local solicited events were resolved by Day 7.

> *Reviewer comment*: Although the results of this study were submitted to support the use of Agriflu in adults and not in children, it is important to note that there were no safety signals observed in the pediatric subgroup. The frequency of local solicited adverse events in subjects 3 to 8 years of age was similar in the two vaccine arms. Grade 3 AEs for local reactions were defined as greater than 100 mm regardless of subject age. Grade 3 local AEs were not reported in children from 3 to 8 years of age for swelling, induration, ecchymosis, or erythema. A reaction of 100 mm or more on a small child would cover much of the subjects arm, and it is possible that use of the same grading scale for small children and adults was not appropriate.

Solicited systemic adverse events for subjects 9 years of age and older are shown in the table below.

Table 22: Study V71P5 – Percentage of Subjects with Individual Systemic Solicited Adverse Events (Subjects 9-17 and 18-64 Years of Age)

		9-17 Years of Age		18-64 Years of Age	
		Agriflu	**Fluvirin**	**Agriflu**	**Fluvirin**
Headache	**Any**	13%	11%	23%	18%
	Severe	0	0	2%	2%
Myalgia	**Any**	9%	13%	14%	16%
	Severe	0	0	1%	1%
Malaise	**Any**	5%	4%	12%	12%
	Severe	<1%	0	1%	1%
Fatigue	**Any**	6%	5%	10%	10%
	Severe	0	0	1%	<1%
Chills	**Any**	5%	6%	5%	7%
	Severe	0	0	<1%	<1%
Arthralgia	**Any**	3%	3%	7%	6%
	Severe	0	0	1%	<1%
Sweating	**Any**	1%	2%	5%	5%
	Severe	0	0	<1%	<1%
Fever	**Any**	<1%	2%	2%	3%
	Severe	0	0	<1%	0

Source: BLA 125297, CSR, Table 12.2.3-3, page 88

The most commonly reported solicited general adverse events in each age cohort were headache and myalgia. The frequency of each solicited general AE was similar in the Agriflu and the Fluvirin arm. The majority of solicited systemic AEs were mild or moderate in intensity. There was one subject in the Agriflu arm with fever of 40º C or higher. This subject had an influenza-like illness with onset two days after vaccination; the fever was judged as vaccine related. Most solicited systemic AEs had resolved by Day 7 with ≤ 3% of adults and ≤ 2% of subjects 9 to 17 years of age reporting solicited AEs at that time point.

> *Reviewer comment:* Solicited systemic adverse events and Grade 3 solicited systemic AEs were more commonly reported in adults than in subjects 9 to 17 years of age. Overall, Grade 3 solicited systemic AEs were uncommonly reported in children from 9 to 17 years of age (2% or fewer subjects).

Solicited systemic adverse events in children 3 to 8 years of age are shown in the table below.

Table 23: Study V71P5 – Percentage of Subjects with Individual Systemic Solicited Adverse Events (Subjects 3-8 Years of Age)

	After 1st Vaccination		After 2nd Vaccination	
	Agriflu	**Fluvirin**	**Agriflu**	**Fluvirin**
Headache	7%	9%	4%	6%
Malaise	5%	6%	5%	4%
Myalgia	5%	5%	5%	5%
Fatigue	4%	5%	3%	2%
Chills	2%	4%	2%	3%
Fever	3%	2%	3%	3%
Sweating	1%	2%	1%	1%
Arthralgia	1%	1%	1%	1%

Source: BLA 125297, CSR, Table 12.2.3-4, page 90

As in older study cohorts, headache was the most commonly reported solicited systemic adverse event in subjects from 3 to 8 years of age.

There was only one Grade 3 solicited systemic AE, so Grade 3 AEs were not shown in the table. This Grade 3 AE was severe malaise reported after the first vaccination in an Agriflu recipient.

> *Reviewer comment*: The frequency of individual solicited systemic adverse events was similar in the two treatment arms, and solicited systemic adverse reactions were slightly less common after the second vaccination. Overall, solicited events were reported less often in children 3 to 8 years of age than in adults. This may be due, in part, to the difficulty that small children may have in articulating some AEs such as myalgia and arthralgia.

Antipyretics or analgesics were used in from 2% to 8% of subjects after vaccination. The percentage of subjects receiving antipyretics / analgesics was 6% for adults in each vaccine arm, 2% of Agriflu recipients and 4% of Fluvirin recipients in the 9-17 year age group, and 8% in Agriflu recipients and 5% in Fluvirin recipients in the 3-8 year age group (after the first vaccination). Two percent of Agriflu recipients in each age group stayed home due to a solicited adverse event. In the Fluvirin group, 2% of subjects 3 -8 years of age, 1% of subjects 9-17 years of age, and 4% of adults stayed home due to a solicited AE.

> *Reviewer comment*: Fewer than 10% of subjects received antipyretics or analgesics post-vaccination. The percentage was similar in Agriflu and Fluvirin recipients. Staying home due to a solicited systemic AE was uncommon in both vaccine arms and in all age groups.

Unsolicited adverse events

Information on unsolicited adverse events was collected for 21 days after vaccination in subjects 9 to 17 years of age and for 28 days post-vaccination in subjects 3 to 8 years of age. The percentage of subjects in each age cohort with unsolicited AEs and serious AEs is shown in the table below.

Table 24: Study V71P5 – Percentage of Subjects with Unsolicited Adverse Events and Serious Adverse Events by Age During the Period 21-28 Days Post-Vaccination

	3-8 Years of Age				9-17 Years of Age		18-64 Years of Age	
	1st vaccination		2nd vaccination					
	Agriflu	Fluvirin	Agriflu	Fluvirin	Agriflu	Fluvirin	Agriflu	Fluvirin
Any	15%	11%	7%	6%	6%	10%	19%	20%
Serious AEs	<1%	0	0	0	<1%	0	0	0

Source: BLA 125297, CSR, Tables 12.2.1-1 and 12.2.1-2, pages 82-83

The percentage of subjects with unsolicited adverse events was similar between the two study arms. The frequency of subjects with unsolicited events was higher in adults than in children. The organ system for which the highest number of unsolicited AEs was reported was Infections and Infestations. The percentage of Agriflu recipients with unsolicited adverse events in the Infections and Infestations organ system was 6% of adults, 4% of subjects 9 to 17 years of age and older, 10% of subjects 3 to 8 years of age after the first vaccination, and 4% after the second vaccination; the percentage of Fluvirin recipients was 7% of adults, 7% of subjects 8 to 17 years of age, 7% of subjects 3 to 8 years of age after the first vaccination, and 3% after the second vaccination. In the two subgroups enrolling subjects younger than 18 years of age, solicited events were not reported at a rate of greater than 2% for any other organ system. Other organ systems for which more than 2% of adult subjects reported unsolicited adverse events were gastrointestinal disorders (4% of Agriflu and 3% of Fluvirin recipients), general disorders (3% of both Agriflu and Fluvirin recipients), and respiratory, thoracic, and mediastinal disorders (4% of Agriflu and 3% of Fluvirin recipients). The types of individual unsolicited AEs reported in at least 2% of adult subjects are shown in the table below.

Table 25: Study V71P5 – Percentage of Subjects 18 to 64 Years of Age with Individual Unsolicited Adverse Events Reported in ≥ 2% of Subjects in Either Vaccine Arm

	Agriflu N=460	Fluvirin N=233
Nasopharyngitis	3%	2%
Influenza-like illness	2%	1%
Headache	2%	1%
Odynophagia	1%	2%
Cough	2%	0
Rhinitis	0	2%

Source: BLA 125297, CSR, Table 12.2.3-6, page 93

As shown in the table above, the majority of the unsolicited adverse events were signs and symptoms of upper respiratory tract infections.

> *Reviewer comment*: The percentage of subjects with individual unsolicited adverse events was low in adults. Most were symptoms of upper respiratory tract infections, and no increase in frequency of AEs from another organ system or cluster of a single category of signs and symptoms were reported. The percentage of individual unsolicited AEs was similar in the two treatment arms.

Two individual adverse events were reported in at least 2% of subjects in either vaccine arm in the cohort of subjects 9 to 17 years of age. These were nasopharyngitis (2% of Agriflu and 3% of Fluvirin recipients) and rhinitis (<1% of Agriflu and 2% of Fluvirin recipients). Bronchitis, nasopharyngitis, and pharyngitis were each reported in more than 2% of subjects from 3 to 8 years of age. Bronchitis was reported in 2% of Agriflu recipients and 3% of Fluvirin recipients after the first vaccination, but in less than 2% of subjects in each arm after the second vaccination. Nasopharyngitis was reported in 2% of Agriflu recipients and 1% of Fluvirin recipients after the first vaccination, but in less than 2% of subjects in each arm after the second vaccination. Pharyngitis was reported in 1% of subjects in each arm after the first vaccination and in 2% of subjects in each arm after the second vaccination.

> *Reviewer comment*: The percentage of subjects younger than 18 years of age with individual solicited adverse events was low. AEs were only symptoms and signs consistent with upper respiratory tract infections. The percentages of subjects with individual solicited adverse events were similar in the two treatment arm. No safety signal was noted.

Medically significant adverse events and serious adverse events

Medically significant events were defined as AEs requiring a physician visit or an emergency room visit and new onset chronic illnesses. Information on medically significant adverse events, serious AEs, adverse events leading to subject discontinuation, and deaths was collected for the entire study period.

In the Agriflu arm, there were 51 subjects (13%) from 3 to 8 years of age, 17 subjects (4%) in the 9 to 17 year age group, and 6 subjects (1%) in the 19 to 64 year age group with medically significant AEs. In the Fluvirin arm, there were 25 subjects (13%) from 3 to 8 years of age, 11 subjects (6%) in the 9 to 17 year age group, and 4 subjects (2%) in the 19 to 64 year age group with medically significant AEs.

The individual types of medically significant events were provided in the study report. The majority of these were infectious or signs/symptoms of acute disease such as vomiting, pharyngitis, pyrexia, pneumonia, and appendicitis. New onset chronic diseases reported included two AEs of diabetes mellitus in the Agriflu arm and one event of ovarian cancer in the Agriflu arm. There were no new chronic illnesses in the Fluvirin arm.

> *Reviewer comment*: The percentage of subjects with medically significant adverse events was low in all arms and was similar in the two vaccine arms. More medically significant adverse events were reported in adults than in subjects younger than 18 years of age. There were no usual AEs or cluster of AEs reported as medically significant events; no safety signal was detected by this reviewer.

The incidence of serious adverse events from Day 21 to study termination is shown below.

Table 26: Study V71P5 – Percentage of Subjects with Serious Adverse Events by Age from Study Day 21 Days after the Last Study Vaccination until Study Termination

	3-8 Years of Age		9-17 Years of Age		18-64 Years of Age	
	Agriflu	**Fluvirin**	**Agriflu**	**Fluvirin**	**Agriflu**	**Fluvirin**
Serious AEs	<1%	2%	1%	0	1%	1%

Source: BLA 125297, CSR, Tables 12.2.1.1-3 and 12.2.1.1-4, pages 84

The Applicant reported the incidence of serious adverse events for the time period from Day 21 to study termination. However, the individual serious adverse events were provided for the entire study period. Three serious adverse events occurred during the 21 days after vaccination. These were:

- An Agriflu recipient in the 9-17 year age cohort was diagnosed with appendicitis on Day 20.
- An Agriflu recipient in the 3-8 year age cohort was diagnosed with an asthma crisis on Day 18.
- An Agriflu recipient in the 3-8 year age cohort was diagnosed with an eye injury on Day 6.

None of these serious AEs were judged to be vaccine-related. There were no serious AEs in the Fluvirin vaccine arm. No adults experienced serious adverse events during the 21 days post-vaccination.

> *Reviewer comment*: All three serious adverse events were reported in the Agriflu arm; however, none of these AEs was likely to be related to the study vaccine.

Serious adverse events occurring more than 21 days after the last study vaccination were reported in 4 subjects from 3 to 8 years of age, 3 subjects from 9 to 17 years of age, and 8 adults. These SAEs are listed below.

- In subjects 3 to 8 years of age:
  - Three Fluvirin subjects were hospitalized due to encephalitis, pneumonia, and vomiting. These were reported from 105 to 181 days after vaccination.
  - One Agriflu subject was hospitalized 83 days after vaccination due to a urinary tract infection.

- In subjects 9 to 17 years of age:
  - Three Agriflu recipients were hospitalized due to renal colic, appendicitis, and vomiting. The onset of these SAEs was from 77 to 178 days after vaccination.

- In subjects 18 to 64 years of age:
  - Six adults who received Agriflu were hospitalized due to SAEs with onset from 42 to 138 after vaccination. The SAEs were diverticulitis, appendicitis, transient decrease in visual acuity, dysentery, ovarian cancer, and spontaneous abortion.

- Two Fluvirin recipients were hospitalized due to syncope, which occurred 103 days post-vaccination, and due to gastritis, which occurred 149 days post-vaccination.

Of the serious adverse events, one was judged as vaccine-related; this was a spontaneous abortion in an Agriflu subject on Day 60. The subject was vaccinated on May 15, 2007; her last menstrual period was April 2, 2007. The subject had an ultrasound performed on July 13, 2007 which confirmed a spontaneous abortion; the exact date of the spontaneous abortion was not known, but she was approximately 14 weeks pregnant at the time of the ultrasound.

> *Reviewer comment:* The number of serious AEs in each vaccine arm was fairly consistent with the 2:1 randomization. The types of serious AEs varied, and there was no increase in a specific organ system or preferred term. Only one SAE was attributed to study vaccine by the investigator. Most SAEs were not temporally related to vaccination. In the opinion of this reviewer, the majority of SAEs did not appear to be related to vaccination.
>
> A spontaneous abortion was reported in a subject. Because conception occurred around the time of vaccination, it is possible that the spontaneous abortion was related to vaccination.

There were no deaths or study discontinuations due to adverse events reported in this study.

8.1.9 Comments & Conclusions

The results for Agriflu met the criteria for demonstration of immunogenicity in adults as outlined in the study protocol. These criteria are described in the FDA Guidance for Industry, "Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines." Specifically, the lower bound of the 95% confidence interval for seroconversion rate was greater than 40% for all three strains and the percentage of subjects with HI titers of 1:40 or higher post-vaccination was greater than 70% for all three strains. In addition, the primary endpoint results were supported by the results of secondary endpoints and subgroup analyses.

The safety results for this study were consistent with the safety data described in the package inserts of other trivalent inactivated vaccines to prevent seasonal influenza. The most commonly reported adverse events were solicited events reported in the week after vaccination. Solicited adverse events reported in 10% or more of adults who received Agriflu were pain at the injection site (25%), headache (23%), myalgia (14%), malaise (12%), and fatigue (10%). Grade 3 solicited AEs were uncommon. The types of unsolicited events, medically significant events, and serious adverse events were varied, and the incidence of individual AEs by preferred term was low. No safety signal was detected by this reviewer.

The Applicant is seeking an indication for adults only. The immunogenicity results for children from 3 to 8 years of age are difficult to interpret due to the high percentage of major protocol

violations in that age group. However, the results in children 9 to 17 years of age were similar to those observed in adult subjects.

8.2 Trial #2 – Study V71P6

A Phase 3, randomized, controlled, observer-blind, single-center study to evaluate the consistency of three consecutive lots of a trivalent subunit influenza vaccine produced in embryonated hen eggs in healthy subjects aged 18-49 years

8.2.1 Objective/Rationale

The primary immunogenicity objective was to demonstrate the immunologic equivalence of three consecutive production lots of Agriflu given to healthy adults aged 18 to 49 years. The secondary immunogenicity objective was to evaluate immunogenicity of the two vaccines (three lots of Agriflu pooled and Fluvirin) and each of the three consecutive production lots of Agriflu by strain-specific antibody response after a single dose of study vaccine.

The safety objectives were to evaluate the safety and tolerability of the three lots of Agriflu pooled and of each production lot of Agriflu for three weeks post-vaccination and to collect serious adverse events, onset of chronic illness, and adverse events resulting in study withdrawal for six months post-vaccination.

8.2.2 Design Overview

This was a Phase 3, randomized, controlled, observer-blind, multi-center study of three lots of Agriflu with Fluvirin as an active comparator. Subjects were randomized at a 2:2:2:1 ratio to receive Agriflu from one of three consecutive lots or to receive Fluvirin. The study was designed to evaluate the consistency, with respect to immunogenicity, of the three consecutive lots of Agriflu. According to the sponsor, the purpose of the active control was to provide a comparative assessment for safety.

Each vaccine dose contained the antigens recommended for the 2007-2008 influenza season in the Northern Hemisphere:
A/Soloman Islands/3/2006 H1N1-like, 15 µg,
A/Wisconsin/67/2005 H3N2-like, 15 µg, and
B/Malaysia/67/2005-like, 15 µg.

Subjects were seen in clinic on Day 1, Day 22, and Day 181. On Day 1, subjects received a single 0.5 mL dose of study vaccine in the deltoid muscle, preferably in the non-dominant arm. Anti-HA antibody titers were collected prior to vaccination on Day 1 and again on Day 22. Local and systemic reactogenicity events occurring on the day of vaccination and during the subsequent six days post-vaccination were recorded on a diary card. Information on all adverse events (AEs) was collected from Days 1 to 22. Information on AEs leading to study

discontinuation, serious AEs, and onset of chronic illness were collected for the entire study period.

8.2.3 Population

Adult subjects who were from 18 to 49 years of age and in good health were enrolled in Study V71P6. Individuals were excluded from study participation if they had received an influenza vaccine or had a laboratory-confirmed influenza illness in the previous six months. Individuals with any impairment of the immune system were also excluded.

8.2.4 Products mandated by the protocol

Subjects were randomized to one of three lots of Agriflu or to Fluvirin in a 2:2:2:1 ratio. Subjects received one 0.5 mL injection of study vaccine, administered in the deltoid muscle. Each dose contained 15 µg of each of the strains recommended for the 2007-2008 influenza season in the Northern Hemisphere:

- A/Soloman Islands/3/2006 H1N1-like, 15 µg,
- A/Wisconsin/67/2005 H3N2-like, 15 µg, and
- B/Malaysia/67/2005-like, 15 µg.

8.2.5 Endpoints

Immunogenicity was assessed by hemagglutination inhibition titer assays using egg-derived influenza antigens. The HI assays were performed by the Clinical Serology Laboratory of Novartis Vaccines.

Lot-to-lot consistency was assessed using bioequivalence: the ratio of Day 22 geometric mean titers (GMTs) was compared between the three lots. Other measures of immunogenicity included percentage of subjects achieving seroconversion or a significant increase in antibody titer at Day 22, percentage of subjects with HI titer $\geq$ 1:40 at Day 1 and Day 22, GMTs at Day 1 and Day 22, and the Day 22/Day 1 geometric mean ratio. Seroconversion was defined as a pre-vaccination HI titer of <10 with a post-vaccination titer $\geq$ 1:40. A significant increase in antibody titer was defined as at least a four-fold increase from a baseline titer of $\geq$ 1:10.

The safety endpoints were local and systemic reactogenicity events, unsolicited adverse events, new onset chronic illnesses and serious adverse events.

8.2.6 Surveillance

Subjects were seen in clinic three times: on Days 1, 22, and 181.

A medical history, physical examination, and vital signs were obtained at the Day 1 study visit. A history-directed physical examination was performed, as needed, at the Day 22 and Day 181

visits. A urine pregnancy test was performed prior to vaccination at the Day 1 visit and again at the Day 22 visit.

Subjects received the study vaccine on Day 1 and were observed for at least 30 minutes after vaccination. Temperature was measured 30 minutes post-vaccination. Diary cards, a digital thermometer, and a ruler were provided on the day of vaccination, and subjects were instructed to record reactogenicity events, concomitant medications, and adverse events on the diary card.

Information on reactogenicity adverse events was collected on the day of vaccine administration and for the subsequent six days. Information was collected on the following local reactogenicity events: ecchymosis, erythema, induration, swelling, and pain at the injection site. The severity of local reactions, except pain, was categorized as none, 1 to ≤10 mm, 11 to ≤25 mm, 51 to ≤100 mm, and >100 mm. Information of the following systemic reactogenicity events was collected: chills, malaise, myalgia, arthralgia, headache, sweating, fatigue, and fever. The severity of pain and systemic reactogenicity events was categorized as none, mild (transient and no limitation on normal daily activity), moderate (some limitation in normal daily activity), and severe (unable to perform normal daily activity). Subjects recorded their daily axillary temperature on the diary card for the 7 days post-vaccination. Fever was defined as an axillary temperature ≥38ºC with severe fever defined as ≥40ºC. Subjects were instructed to record any days that they stayed home due to reactions and the use of analgesic / antipyretic medication to treat reactions.

Information on unsolicited AEs was collected for the first 22 days of the study. Information on serious AEs and new chronic illnesses was collected from Day 22 to Day 181.

8.2.7 Statistical considerations

Study V71P6 was an observer-blind study. Designated unblinded study personnel were responsible for administration of the study vaccines and for vaccine accountability. These personnel were not involved in trial conduct or monitoring and did not have access to subjects' case report forms.

The active control arm was included to provide a comparative assessment for safety rather than immunogenicity.

Populations analyzed in this study were defined below:

- All enrolled population – all subjects with demographic data
- Full Analysis Set / Modified Intention-to-Treat (MITT) Population, Immunogenicity – all subjects who received the study vaccination and provided evaluable serum samples at baseline and post-vaccination
- Per Protocol population, Immunogenicity – all subjects in the Full Analysis Set who received the correct dose of the correct vaccine, provided evaluable serum samples at baseline and post-vaccination, and who had no major protocol violation identified prior to unblinding

- Exposed population – all subjects who received study vaccination
- Safety population – all subjects in the exposed population with post-vaccination safety data

Lot-to-lot consistency (the primary endpoint) was analyzed using bioequivalence. The ratio of Day 22 geometric mean titers (GMTs) was calculated and compared between the three lots. For lot-to-lot consistency to be demonstrated, the two-sided 95%CI for ratios of GMTs on Day 22 had to be within the equivalence range, defined as 0.67-1.5. The sample size was chosen to demonstrate that the ratios of Day 22 GMTs between the three vaccine lots were equal to 1.0 with the lower and upper limits of the 95% confidence interval in the range of 0.5 to 2.0. The overall power was 90%.

Other measures of immunogenicity were secondary endpoints and included the percentage of subjects achieving seroconversion or a significant increase in antibody titer at Day 22, the percentage of subjects with HI titer ≥ 1:40 at Day 1 and Day 22, GMTs at Day 1 and Day 22, and the Day 22/Day 1 geometric mean ratio (GMR). Seroconversion was defined as a pre-vaccination HI titer of <1:10 with a post-vaccination titer ≥ 1:40. A significant increase in antibody titer was defined as a four-fold or greater increase from a baseline titer of ≥ 1:10.

The percentage of subjects with HI titers of 1:40 or higher post-vaccination, with seroconversion or significant increase in HI titers were considered statistically compliant with the FDA Guidance for Industry, "Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines" if:

- the lower limit of the 95% confidence interval (CI) for the percentage of subjects with seroconversion or significant increase in HI antibody titer met or exceeded 40%
- the lower limit of the 95% CI for the percentage of subjects achieving an HI antibody titer ≥40 met or exceeded 70%.

Local and systemic reactogenicity events were summarized as none versus any. Differences among the vaccine groups were analyzed by using Pearson's chi-square test or Fisher's Exact test where appropriate. All adverse events were coded using the MedDRA dictionary. Data regarding AEs were summarized using descriptive statistics.

8.2.8 Results

The first subject was enrolled on November 12, 2007 and the last Day 22 study visit was completed on December 21, 2007. Long-term safety follow up (from Day 23 to Day 181) was not included in this study report.

The study was conducted in Santo Domingo, Republica Dominicana at two study sites: the Hospital Maternidad Nuestra Senora de la Altagracia and the Centro Sanitario de Santo Domingo. Both sites were under the supervision of a single principal investigator, Luis Rivera, M.D.

8.2.8.1 Populations enrolled/analyzed

A total of 1507 adults were enrolled and randomized in Study V71P6: 1290 in the Agriflu arms and 217 in the Fluvirin arm. Of these, 1277 subjects in the Agriflu arms and 216 in the Fluvirin arm were vaccinated. Subject disposition and the different study populations are shown in the table below.

Table 27: Study V71P6 - Patient Distribution and Resulting Study Populations

	Lot A	Lot B	Lot C	All Agriflu	Fluvirin
Enrolled	430	431	429	1290	217
Didn't meet entry criteria	5	4	1	10	1
Consent withdrawn	2	1	0	3	0
Vaccinated	423	426	428	1277	216
Received wrong vaccine	-1/+3	-2/+1	-4/+4	-2/+3	-3/+2
Total Exposed	425	425	428	1278	215
Consent withdrawn	12	5	12	29	4
Lost to follow-up	10	16	14	40	9
Unknown	1	0	1	2	0
Made Day 22 Visit	402	404	401	1207	202
Major protocol violation	9	8	8	25	8
Per Protocol Population	393	396	393	1182	194
Safety Population	403	404	402	1209	202

*Ten subjects got the wrong vaccine but were included in safety analysis of vaccine actually received. These included seven subjects in the Agriflu arm: five of whom received the wrong lot of Agriflu and two who received Fluvirin instead of Agriflu.
Source: BLA 125297, CSR, Tables 10.1-1 and 1.1-1, Figures 10.1-1 and 10.1-2, pages 40-45

As shown in the table above, the most common reason for subjects to be excluded from the Per Protocol population was loss to follow-up, which was reported for 40 Agriflu recipients and 9 Fluvirin recipients. The safety population excluded 96 subjects who had no safety data after discharge from clinic (82 Agriflu and 14 Fluvirin).

> *Reviewer comment*: On analysis of the information provided, after taking into account the 2:2:2: 1 randomization, the number of subjects with premature study discontinuation was similar between the two vaccine groups.

Protocol violations

Major protocol violations were reported for 131 subjects (8.7%): 109 in the Agriflu arms and 22 in the Fluvirin arm.

Table 28: Study V71P6 - Major Protocol Violations

	Agriflu	Fluvirin
Consent withdrawn	32	4
No Day 22 visit	84	14
Lost to follow-up	40	9
Did not meet entry criteria	12	2
Outside age criteria	3	1
Received wrong vaccine	8	2
Did not receive assigned vaccine	12	1
Blood draw outside window	2	0
No Day 1 blood draw	5	0
No Day 22 blood draw	13	5

Source: BLA 125297, CSR, Text, pages 43-44

The most common major protocol violations were no Day 22 visit, consent withdrawn, and loss to follow up.

There were an additional 216 subjects (14%) with minor protocol violations. These included 286 subjects with low body temperatures, 78 subjects with the second blood draw outside of the window period, 11 subjects who were withdrawn on Day 1 because of inappropriate enrollment and nine subjects who became pregnant in the 21 days between the first and second study visits.

> *Reviewer comment*: Major protocol violations were reported for 8.7% of subjects. The types and number of protocol violations were similar between the two vaccine groups after accounting for randomization. It is unclear why so many subjects had low body temperatures, and it may reflect on the adequacy of subject training in the use of thermometers.

Additional study conduct issues

CBER was notified by the Applicant on September 22, 2008 that there were problems with the oversight of the study sites for Study V71P6 by the local ethics committee. Specific problems cited by the sponsor were as follows.

- Original documents, including protocol amendments, informed consents, and serious adverse event reports, were destroyed.
- Personnel issues within the Ethics Committee included that the head of the Ethics Committee was unaware of the procedures and policies of the Ethics Committee, there were discrepancies in dates and in participating members on Ethics Committee documents, and there was no documentation of the qualifications and credentials of Ethics Committee members.
- Serious adverse event reports were sent to the Ethics Committee on a monthly basis instead of within five days as outlined in the study protocol.

There was a second, national Institutional Review Board monitoring the study, CONABIOS. The Applicant is not aware of any problems with oversight by CONABIOS.

Because of these IRB issues, CBER requested information about the Applicant's site monitoring; these data were submitted to CBER on October 17, 2008. The two study sites were initially assessed by Novartis at pre-study visits on June 27, 2007 (site 10) and September 18-21, 2007 (sites 10 and 11). Subsequent study visits were conducted by Novartis and by the contract organization on October 25, 2007 and on November 6, 2007 for study site training. Additional visits were made on November 12, 2007 for enrollment of the first study subject. Weekly visits were made after that date; however, the exact dates of the weekly visits were not recorded. A routine GCP audit was conducted at both sites on February 28-29, 2008. The IRB was inspected on August 20-22, 2008.

Issues identified during monitoring visits by the Applicant included:

- Protocol deviations in 23% of subjects due to incorrect use of thermometers with low body temperature recorded (10%), visits outside the study window (5%), loss to follow-up (3%), withdrawn consent (2%), refusal of blood draw (2%), not meeting entry criteria (0.8%), assigned the wrong vaccine (0.7%), and positive pregnancy test (0.6%).
- There was a lack of documentation and verification of informed consents. Some informed consent forms were not dated by the subjects, and some subjects were not provided with a copy of their consent. Issues with informed consent were reported in 121 subjects (8%).
- Diary cards were lost or only partially completed due to loss to follow-up or withdrawn consent.

As a result of these findings, the primary investigator and his staff were retrained on the protocol, informed consent requirements, and clinical trial procedures. A total of 868 subjects were enrolled prior to re-training, and 639 were enrolled after re-training.

The two study sites for V71P6 were inspected by CBER Bioresearch Monitoring Program. Please see Mr. Wesley's review. In brief, the BIMO inspector issued a FDA-483 for the following issues:

51 subjects were enrolled at a study site not listed on the Form FDA 1572. This site was the b(4)---- factory; the site was not authorized by Novartis.

- Physical examinations to assess eligibility were not consistently performed. Examples provided for this were abdominal examinations performed while subjects were seated in a chair, lack of an otoscope, and inconsistent monitoring of blood pressure.
- Axillary temperatures were not obtained at visit #2.
- Source documents lack sufficient detail to determine if physical examinations were performed.

The BIMO inspector also reported that eight subjects had positive pregnancy tests at screening. However, the inspector did note that there was no evidence of under-reporting of adverse events,

and that there were no discrepancies between the source documents, CRFs, and the data submitted in the BLA.

The Applicant performed a sensitivity analysis of immunogenicity results excluding the 51 subjects from the unregistered study site. The results of the lot-to-lot consistency analysis and of the analysis of secondary endpoints (seroconversion rate and percentage of subjects with post-vaccination HI titers ≥ 1:40); the immunogenicity conclusions were unchanged. The Applicant reported the safety results for the 51 subjects. The percentage of subjects with premature study discontinuation was higher at this site (18 of 51 or 35% withdrew prematurely compared to 5% at the authorized sites). All 18 subjects withdrew due to withdrawn consent. Three percent of subjects at the unregistered site had local solicited adverse reactions and 18% had general solicited adverse reactions. According to the Applicant, the unsolicited AEs reported were similar to those at the authorized site. Finally, there were no serious AEs reported at the unregistered site.

> *Reviewer comment*: The findings of the BIMO inspector bring the safety monitoring of this study into question. However, there was no evidence of under-reporting or of inconsistencies between the data submitted to CBER and the source documents. Therefore, these safety data should be acceptable for inclusion in the package insert and for analysis of Agriflu safety. In addition, the results for multiple other studies were submitted and can be used to support findings in Study V71P6. There are no concerns with the immunogenicity data.

Demographics
The demographic characteristics for the Enrolled population are shown in the table below.

Table 29: Study V71P6 – Study Demographics for Enrolled Population

	Agriflu N=1290	Fluvirin N=217
Mean Age (years)	31.2	31.3
% Female	70%	71%
Race		
Hispanic	97%	99%
Black	2%	1%
White	<1%	0
Arabic	<1%	0
Native American/Alaskan	<1%	0
No prior flu vaccination	99.9%	99.9%

Source: BLA 125297, CSR, Table 11.2-1, page 46

The mean age for subjects in each Agriflu lot arm and in the Fluvirin arm was 31 years. Seventy percent of subjects in the Agriflu arms were female; the percentage of females in each lot arm was similar and ranged from 68% to 72%. The overwhelming majority of study subjects were Hispanic. Almost all subjects had never been previously vaccinated against seasonal influenza.

Reviewer comment: The demographics of the study population reflect the study site and are not consistent with the overall U.S. population. However, there is no known difference in influenza vaccine immunogenicity or clinical efficacy by race.

Demographic data for the Immunogenicity Per Protocol population and for the Safety population were similar to that shown in the table above for the Enrolled population. The average age in all three populations was 31 years. The percentage of females in either of the vaccine arms for the three populations ranged from70%-73%. The percentage of Hispanic subjects ranged from 97%-99%.

8.2.8.2 Efficacy endpoints/outcomes

The primary immunogenicity objective was demonstration of immunologic equivalence for the three consecutive production lots of Agriflu administered to healthy adults aged 18 to 49 years. This was determined by comparing the ratio of Day 22 geometric mean titers (GMTs) between the three lots. For lot-to-lot consistency to be demonstrated, the two-sided 95% CI for ratios of GMTs on Day 22 had to be within the equivalence range, defined as 0.67-1.5. Results of the lot-to-lot bioequivalence analysis are shown below.

Table 30: Study V71P6 – Two-Sided 95% Confidence Intervals for Ratios of Day 22 Geometric Mean Titers between Lots of Agriflu

	Lot A/B	**Lot A/C**	**Lot B/C**
A/H1N1	0.92-1.29	0.93-1.31	0.85-1.2
A/H3N2	0.97-1.3	0.85-1.13	0.76-1.01
B	0.91-1.23	0.99-1.33	0.94-1.26

Source: BLA 125297, CSR, Table 11.4.1-1, page 48

As shown in the table above, the two-sided confidence intervals for each pair-wise comparison were between the pre-defined range of 0.67 to 1.5; therefore, lot-to-lot consistency was demonstrated.

Secondary immunogenicity endpoints
Secondary immunogenicity endpoints included seroconversion to all three strains, percentage of subjects with HI titers of 1:40 or higher to all three strains, GMTs at Day 1 and at Day 22, and GMR (defined as ratio of geometric mean titers of Day 22 to Day 1). The results for each of these endpoints are shown in the table below.

Table 31: Study V71P6 – Results for Secondary Immunogenicity Endpoints:

	Agriflu (N=1182)			Fluvirin (N=194)		
	A/H1N1	**A/H3N2**	**B**	**A/H1N1**	**A/H3N2**	**B**
Baseline GMT	16	47	6.7	16	44	6.8
Baseline % w/ HI≥1:40	32%	64%	4%	31%	62%	3%
Seroconversion Rate	94%	67%	84%	96%	84%	86%
LL 95%CI*	93%	65%	82%	92%	78%	80%
% of Subjects w/ HI ≥1:40	98%	99%	87%	98%	99%	90%
LL 95%CI*	97%	98%	85%	95%	97%	85%
Day 22 GMT	532	341	93	799	683	99
GMR	34	7.3	14	50	15	15

*LL 95% CI is the lower limit of the 95% confidence interval.
Source: BLA 125297, CSR, Table 11.4.1.2.1-1, page 50

As shown in the table above, the HI titers at baseline were similar between arms for each strain. The percentage of subjects with a baseline HI titer of 1:40 or greater was also similar between arms for each strain. The baseline HI titers and the percentage of subjects with a HI titer ≥ 1:40 were highest for the influenza A/H3N2 strain and lowest for the influenza B strain.

Seroconversion was defined as a pre-vaccination HI titer of <1:10 with a post-vaccination titer ≥ 1:40. A significant increase in antibody titer was defined as a four-fold or greater increase from a baseline titer of ≥ 1:10. The results for both of these variables are shown in the table above for seroconversion. The lower bound 95% confidence interval for seroconversion rate was greater than 40% for both arms and all three strains. In the Agriflu arms, the lower bound of the 95% confidence interval for each lot ranged from 90-92% for influenza A/H1N1, 59-62% for influenza A/H3N2, and 76-81% for influenza B. These results were very similar to that reported in the Fluvirin arm.

> *Reviewer comment*: These results met the criteria recommended for seroconversion as described in the FDA Guidance for Industry, "Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines." The criteria for demonstration of immunogenicity with seroconversion is a post-vaccination lower bound of the 95% seroconversion rate of 40% or greater.
>
> The higher seroconversion rate for influenza A/H1N1 and influenza B strains may have been due to the lower baseline titers; baseline titers that are low at baseline are more likely to increase four fold than titers that are already high.

As defined in the FDA Guidance, immunogenicity is demonstrated if the percentage of subjects with post-vaccination HI titers of 1:40 or greater is 70% or higher. The percentage of subjects with post-vaccination HI titers was greater than 70% in both arms and for all three strains. In the three Agriflu lots, the seroconversion rate ranged from 96-98% for both influenza A strains and 80-85% for influenza B. The results were similar for the pooled Agriflu arms and the Fluvirin arm.

Reviewer comment: The percentage of subjects with HI titers of 1:40 or greater post-vaccination was higher for the influenza A strains than for the influenza B strain. This is likely due to the lower influenza B titers at baseline.

Geometric mean titers were substantially higher post-vaccination compared to baseline. In the pooled Agriflu arms, the fold increase in titers from baseline (GMR) was 34 for influenza A/H1N1, 7.3 for influenza A/H3N2, and 14 for influenza B. In the Fluvirin arm, the fold increase from baseline was 50 for influenza A/H1N1, 15 for influenza A/H3N2, and 15 for influenza B.

Reviewer comment: The increases in GMT were substantial and the fold increase ranged from 7.3 fold for Agriflu against influenza B to 50 fold for Fluvirin against influenza A/H1N1. The higher fold increases for influenza A/H1N1 were likely due to the lower baseline titers.

Subgroup analyses

Immunogenicity results by gender are shown in the table below.

Table 32: Study V71P6 – Lower Bound 95% Confidence Interval for Percentage of Subjects with Seroconversion and with HI Titers ≥ 1:40 Post-Vaccination by Gender

Influenza Strain	**Agriflu**		**Fluvirin**	
	Male	**Female**	**Male**	**Female**
Seroconversion Rate				
H1N1	90%	93%	90%	90%
H3N2	60%	65%	62%	80%
B	80%	81%	68%	81%
Percent with HI Titers ≥ 1:40 Post-Vaccination				
H1N1	97%	97%	93%	93%
H3N2	97%	98%	90%	97%
B	84%	84%	72%	86%

Source: BLA 125297, CSR, Tables 14.2.1.1.3 and 14.2.1.2.3, pages 124-129 and 142-147

Reviewer comment: In general, the immunogenicity results were similar for males and for females in both study arms. The seroconversion rate against the influenza H3N2 strain was higher for females in the Fluvirin arm than for male Fluvirin recipients or for either gender in the Agriflu arm. This may be due in part to differences in baseline values; the percentage of subjects with HI titers of 1:40 or greater at baseline was 53% in females and 62% in males in the Fluvirin arm. However, it is more likely due to chance as may be observed in analyses of multiple subgroups, because the difference by gender was not observed in the Agriflu arm. The seroconversion rate against influenza B was similar in males and females in the Agriflu arm and females in the Fluvirin arm but lower in males in the Fluvirin arm. Again, the reason for this gender difference in the Fluvirin is

unclear, and it cannot be explained by baseline percentage of subjects with HI titers ≥ 1:40. While the differences by gender may be due to statistical chance, a gender difference in response to influenza B in Fluvirin recipients cannot be ruled out.

8.2.8.3 Safety outcomes

The V71P6 safety results were provided for the first 22 days of the study. The safety results from Day 22 to study termination will be submitted at a later date.

A total of 1411 subjects were included in the safety analysis: 1209 in the Agriflu arms and 202 in the Fluvirin arm.

Solicited adverse events
Information on solicited adverse events was collected for the day of vaccination and for the six subsequent days (seven days total). The percentage of subjects with any solicited adverse event is shown below for each Agriflu arm, the pooled Agriflu arms, and the Fluvirin arm.

Table 33: Study V71P6 - Percentage of Subjects with Solicited Adverse Events

	Agriflu Lots				
	Lot A (N=403)	**Lot B (N=404)**	**Lot C (N=402)**	**All Agriflu (N=1209)**	**Fluvirin (N=202)**
Any	47%	45%	46%	46%	44%
Local	28%	24%	25%	26%	27%
General	37%	37%	37%	37%	38%
Other*	11%	14%	14%	13%	14%

*Other = stayed home due to solicited AE, fever, and use of analgesics/antipyretics
Source: BLA 125297, CSR, Table 12.2.1-1, page 58

As shown in the table above, the percentage of subjects with any solicited adverse event or with a local or general solicited adverse event was similar between the three Agriflu lots. In addition, the results for the pooled lots were similar to results observed in the Fluvirin arm.

Reviewer comment: The percentages of subjects with any solicited AE, local solicited AEs, and other were lower in both arms of this study compared to what was observed in Study V71P5. The percentage of subjects with solicited general AEs was higher in Study V71P5. It is unclear why there were fewer local solicited AEs or any AEs in Study V71P6. One possible explanation for fewer subjects staying home or using analgesics/antipyretics in Study V71P5 may be that this study was conducted in a resource poor country, where decisions to stay home from work or to take medications may be related to economic conditions.

Local solicited AEs were reported at a similar frequency in the three lots of Agriflu. The differences in incidence of individual solicited adverse events between the lots were 3%

or less.

Reviewer comment: The results by Agriflu lot were similar, so additional safety results are provided for the pooled Agriflu arms only.

The percentage of subjects with individual solicited local adverse events is shown in the table below.

Table 34: Study V71P6 - Percentage of Subjects with Individual Solicited Local Adverse Events

	Agriflu N=1209	**Fluvirin N=202**
Any Pain	22%	22%
Grade 3	<1%	1%
Any Induration	5%	6%
Any Swelling	4%	7%
Any Erythema	4%	4%
Any Ecchymosis	3%	4%

Source: BLA 125297, CSR, Table 12.2.3-1, page 60

The most commonly reported local solicited adverse event was pain, which was reported in 22% of subjects in the pooled Agriflu arms and the Fluvirin arm. Grade 3 pain was reported uncommonly (1% or fewer subjects). Erythema, induration, swelling and ecchymosis were all reported in fewer than 10% of subjects; there were no Grade 3 AEs reported for any of these local solicited AEs.

Reviewer comment: The percentage of subjects with each individual local solicited AE was lower in this study as compared to Study V71P5. The reason for fewer local solicited AEs in this study is unclear to this reviewer. The differences were observed in both vaccine arms; therefore, there was no bias toward Agriflu. However, it does raise concerns about interpretation of local reactions by the subjects and study personnel in Study V71P6. However, the CBER BIMO inspector did not identify any issues with adverse event collection.

The occurrence of solicited local AEs peaked between Days 1 and 3. On day 7, ≤ 1% of subjects had solicited local AEs.

The percentage of subjects with individual solicited general events is shown in the table below.

Table 35: Study V71P6 - Percentage of Subjects with Individual Solicited Systemic Adverse Events

	Agriflu	Fluvirin
Any Headache	24%	25%
Grade 3	1%	2%
Any Myalgia	18%	20%
Grade 3	1%	<1%
Any Malaise	12%	12%
Grade 3	1%	<1%
Any Fatigue	9%	8%
Grade 3	<1%	<1%
Any Chills	7%	8%
Grade 3	1%	0
Any Arthralgia	6%	7%
Grade 3	<1%	0
Any Sweating	4%	4%
Any Fever (≥38ºC)	4%	3%
Grade 3 (≥40ºC)	<1%	0
Analgesics/Antipyretics	9%	9%
Stayed Home due to AE	7%	9%

Source: BLA 125297, CSR, Table 12.2.3-2, page 63

The most commonly reported solicited systemic adverse event was headache, which was reported in approximately one-fourth of subjects in the Agriflu arms and in the Fluvirin arm. Myalgia was reported in 18% of Agriflu recipients and in 20% of Fluvirin recipients; malaise was reported in 12% of subjects in both vaccine groups. All other solicited systemic AEs were reported in fewer than 10% of subjects.

Most solicited systemic adverse events were mild or moderate in intensity; the percentage of subjects with any Grade 3 solicited general AEs was 1% or less for all AEs. Two subjects reported a fever of 40ºC or higher; both were in the Agriflu group, and both were judged as possibly related to study vaccine.

> *Reviewer comment:* Although only two subjects reported temperatures of 40ºC or higher, temperatures were taken in the axilla and represent a higher actual core body temperature. The use of 40ºC as Grade 3 axillary temperatures may underestimate the percentage of subjects with fever and with Grade 3 fever.

The occurrence of solicited systemic AEs peaked from Days 1 to 4.

Nine percent of subjects in each vaccine group used analgesics or antipyretics in the seven days after vaccination. Seven percent of Agriflu recipients and 9% of Fluvirin recipients stayed home due to a solicited adverse event.

Reviewer comment: The percentage of subjects with individual solicited systemic adverse events was similar in the two vaccine groups. Solicited systemic adverse events were reported in a slightly higher percentage of subjects in Study V71P6 compared to V71P5. The difference was primarily due to an increase in the number of subjects with headache (reported in 24% of both Agriflu and Fluvirin recipients in V71P6 compared to 23% of Agriflu recipients and 18% of Fluvirin recipients in V71P5) and with myalgia (reported in 18% of Agriflu recipients and 20% of Fluvirin recipients in V71P6 compared to 14% of Agriflu recipients and 16% of Fluvirin recipients in V71P5). These differences were small and are unlikely to be meaningful.

Unsolicited adverse events

Unsolicited adverse events were reported in 16% of both Agriflu and Fluvirin recipients during the first 22 days of the study. The percentage of subjects in the three Agriflu lots with unsolicited AEs was similar (14 – 17%). Unsolicited events by organ system are shown in the table below.

Table 36: Study V71P6 - Percentage of Subjects with Unsolicited AEs by Organ System:

	Agriflu	**Fluvirin**
Cardiac	<1%	0
Ear and Labyrinth	<1%	<1%
Endocrine	<1%	0
Eye	<1%	1%
Gastrointestinal	2%	2%
General and Admin Site	7%	5%
Hepatobiliary	0	<1%
Immune System	<1%	<1%
Infections and Infestations	1%	3%
Injury and Poisoning	<1%	0
Musculoskeletal / Connective Tissue	2%	0
Nervous System	4%	2%
Psychiatric	<1%	0
Reproductive and Breast	<1%	0
Respiratory, Thoracic, Mediastinal	3%	2%
Skin and SC Tissue	<1%	0
Surgical and Medical Procedure	<1%	0
Vascular	<1%	0

Source: BLA 125297, CSR, Table 12.2.3-3, page 64

As shown in the table above, organ systems in which more than 2% of subjects had unsolicited AEs during the first 22 days of the study were general and administrative sites, nervous system, and respiratory, thoracic, and mediastinal. The most frequently reported individual unsolicited AEs (those reported in ≥ 2% of subjects in either arm) were:

- Influenza-like illness (4% of subjects in both arms)
- Headache (3% of Agriflu subjects and 2% of Fluvirin subjects), and
- Pharyngeal pain (2% of Agriflu subjects and <1% of Fluvirin subjects).

Reviewer comment: The adverse event dataset was analyzed for cases identified as oculorespiratory syndrome, but none were found. There were seven AEs of conjunctivitis. All but one was reported on Day 5 or later. One event of conjunctivitis was reported on Day 2 but was not associated with respiratory symptoms.

Unsolicited adverse events that were judged as possibly related to study vaccine were reported in 8% of Agriflu recipients and 7% of Fluvirin recipients. The most frequently reported unsolicited event judged as possibly vaccine related was influenza-like illness, which was reported in 2% of both Agriflu and Fluvirin recipients.

Reviewer comment: Unsolicited adverse events were reported at similar rates in the two vaccine arms. There was no increase in any individual solicited AEs or in clusters of related AEs.

Sixteen serious adverse events were reported in 12 subjects. Individual serious AEs are listed in the table below

Table 37: Study V71P6 - Serious Adverse Events by Treatment Arm

Agriflu			**Fluvirin**
Lot A	**Lot B**	**Lot C**	
Abortion – induced	Abortion - induced	Fever/ Headache*	Cholecystitis
Spontaneous abortion*	Abortion - spontaneous	Cholelithiasis	Fibroadenoma
Goiter	MVA# with Sp. Abortion	--	--
MVA#	Uterine myoma	--	--
--	Hysterectomy	--	--

#MVA=motor vehicle accident
*judged as possibly vaccine-related
Source: BLA 125297, CSR, Table 12.3.1.2-1, page 67

Two serious adverse events were judged as possibly related to study vaccine. Both subjects received Agriflu. These two SAEs are described below.

- A 20 year old female in the Lot A group was vaccinated with Agriflu on November 20, 2007. Her last menstrual period was 18 days prior to vaccination. She experienced a spontaneous abortion at approximately 14 weeks gestation (study Day 58). The subject completely recovered. The SAE was considered vaccine related because of the temporal relationship of vaccination and conception.
- A 21 year old female in the Lot C group was vaccinated with Agriflu on November 15, 2007. Approximately 7 hours later, she developed a severe headache with Grade 3 fever and was hospitalized. She was treated with acetaminophen and ceftriaxone for possible infection. The subject completely recovered and was discharged four days later.

Reviewer comment: Serious adverse events were uncommon in the study. Although there were three spontaneous abortions, one was related to a motor vehicle accident. Although one-half of the SAEs were related to the reproductive system, that is not surprising due to the high proportion of women participating in the study. Two SAEs were judged as possibly related to study vaccine, and both were temporally related to vaccination and vaccine-relatedness cannot be ruled out.

There were no study deaths and no discontinuations due to AEs.

8.2.9 Comments & Conclusions

In Study V71P6, lot-to-lot consistency for three lots of Agriflu was demonstrated. In addition, the immunogenicity results for the 3 pooled Agriflu lot groups met the criteria used by CBER to define successful demonstration of immunogenicity for all three vaccine influenza strains. There were no safety signals identified in the review of this study. The interpretation of safety data is complicated because of the lower percentage of subjects with solicited adverse events reported in this study and the problems with safety monitoring identified at a BIMO inspection. However, it was reassuring that on inspection there was no under-reporting of AEs and the data submitted to CBER was consisted with that in the source documents.

8.3 Additional Studies Supporting Efficacy

The results of two additional studies were included in this BLA to support Agriflu immunogenicity: Study V58P4 and Study V58P9. In both of these studies, Agriflu served as the active control, and the test vaccine was a cell-derived seasonal influenza vaccine. The results of a third study, Study V58P2, were requested by CBER since the study design of V58P2 was almost identical to that of V58P4. The study results are presented in the chronological order in which the studies were conducted.

Study V58P2

A Phase II, observer-blind, randomized, single-center study to evaluate safety, tolerability, and immunogenicity of a single intramuscular dose of trivalent subunit influenza vaccine produced either in mammalian cell culture or in embryonated hen eggs, in healthy adult subjects

Study Design

The safety objective was to evaluate the safety and tolerability of a single, intramuscular 0.5 mL injection of cell culture-derived and egg-derived influenza subunit vaccines. The immunogenicity objective was to evaluate the immunogenicity of a single, intramuscular 0.5 mL dose of the cell culture-derived and egg-derived influenza subunit vaccine, in compliance with the requirements of the current European Union recommendations (CPMP/BWP/214/96).

This was a Phase II, randomized, controlled, observer-blind study of the safety and immunogenicity of a cell-derived influenza vaccine. Healthy adult volunteers were stratified by age (18-60 years and ≥ 61 years) and randomized to receive a single dose of either the cell-derived vaccine or Agriflu. The vaccine was administered as a 0.5 mL dose in the deltoid muscle, preferably of the non-dominant arm. Antibody response was measured pre-vaccination and on Day 22 post-vaccination.

Each vaccine dose contained the antigens recommended for the 2003 influenza season in the Southern Hemisphere:
A/New Caledonia/20/99 H1N1-like, 15 µg,
A/Panama/2007/99 H3N2-like, 15 µg, and
B/Shangdong/7/97-like, 15 µg.

Subjects were seen in clinic on Day 1 and Day 22. On Day 1, subjects received a single 0.5 mL dose of study vaccine. Anti-HA antibody titers were collected prior to vaccination on Day 1 and again on Day 22. Local and systemic reactogenicity events occurring on the day of vaccination (from six hours post-vaccination) and during the six days post-vaccination were recorded on a diary card. Information on all other adverse events (AEs) was collected from Days 1 to 22.

Adult subjects who were from 18 years of age and older and in good health were enrolled in Study V58P2. Individuals were excluded from study participation if they had received an influenza vaccine or had laboratory-confirmed influenza in the previous six months. Individuals were also excluded for acute illness, history of hypersensitivity to any component of the study vaccine, history of serious vaccine reactions, or history of allergy to eggs or egg products, and for any impairment of the immune system

Immunogenicity was determined by hemagglutination inhibition titers using egg-derived influenza antigens. Single radial hemolysis was also used to measure antibody response. CBER recommends use of hemagglutination inhibition titers in the FDA Guidance for Industry, "Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines;" therefore these results, and not single radial hemolysis, are presented in this review. Immunogenicity was evaluated using CHMP criteria for seroconversion or significant increase in antibody titer, for geometric mean ratio, and for percentage of subjects with HI titers of 1:40 or more post-vaccination. Seroconversion was defined as a pre-vaccination HI titer of <1:10 with a post-vaccination titer ≥ 1:40, and a significant increase was defined as at least a four fold increase in HI titer from Day 1 to Day 22.

Subjects were seen in clinic twice: on Days 1 and 22; there was no follow up past Day 22. Subjects were contacted on Day 3 by telephone to assess adverse events. A medical history, physical examination, and vital signs were obtained at the Day 1 study visit. The physical examination was repeated at the Day 22 visit.

Subjects received the study vaccine on Day 1 and were observed for at least 30 minutes after vaccination. Information on reactogenicity adverse events was collected on the day of vaccine administration and for the subsequent six days.

- Information was collected on the following local reactogenicity events: ecchymosis, erythema, induration, swelling, and pain at the injection site. The severity of local reactions, except pain, was categorized as none, 1 to ≤10 mm, 11 to ≤25 mm, 51 to ≤100 mm, and >100 mm.
- Information on the following systemic reactogenicity events was collected: chills, malaise, myalgia, arthralgia, headache, sweating, fatigue, and fever. The severity of pain at the injection site and systemic reactogenicity events was categorized as none, mild (transient and no limitation on normal daily activity), moderate (some limitation in normal daily activity), and severe (unable to perform normal daily activity). Subjects recorded their daily axillary temperature on the diary card for the 7 days post-vaccination. Fever was defined as an axillary temperature ≥38ºC with severe fever defined as ≥40ºC.

Information on all other adverse events (unsolicited AEs) was collected for the first 22 days of the study. No safety laboratory testing was performed.

Safety was evaluated by information on adverse events, including solicited adverse reactions. Statistical analyses of these AEs were descriptive.

> *Reviewer comment*: Agriflu was compared to an investigational vaccine in these studies. Therefore, any safety results are limited by the lack of a U.S. licensed comparator.

Measures of immunogenicity were secondary endpoints and included the percentage of subjects achieving seroconversion or a significant increase in antibody titer at Day 22, percentage of subjects with HI titer ≥ 1:40 at Day 1 and Day 22, GMTs at Day 1 and Day 22, and the Day 22/Day 1 geometric mean ratio. Seroconversion was defined as a pre-vaccination HI titer of <1:10 with a post-vaccination titer ≥ 1:40. A significant increase in antibody titer was defined as a four-fold or higher increase from a baseline titer of ≥ 1:10.

The percentage of subjects with HI titers of 1:40 or higher post-vaccination, with seroconversion or significant increase in HI titers were evaluated using the CPMP Note for Guidance on Harmonisation of Requirements for Influenza Vaccines (CPMP/BWP/214/96). The criteria for demonstration of immunogenicity in this European Guidance include:
For adults 18 to 60 years of age,

- the percentage of subjects with seroconversion or significant increase in HI antibody titer should meet or exceeds 40%
- the percentage of subjects achieving an HI antibody titer ≥40 post-vaccination should meet or exceeds 70%, and
- the geometric mean increase in antibody titer should be greater than 2.5.

For adults 61 years of age or older,

- the percentage of subjects with seroconversion or significant increase in HI antibody titer should meet or exceeds 30%

- the percentage of subjects achieving an HI antibody titer ≥40 post-vaccination should meet or exceeds 60%, and
- the geometric mean increase in antibody titer should be greater than 2.0.

As described in the CPMP recommendations, these criteria must be met for one of the three influenza vaccine strains for the vaccine to demonstrate immunogenicity.

Reviewer comment: The criteria recommended in the CPMP Note for Guidance of Harmonisation of Requirements for Influenza Vaccines differ slightly from those recommended in the FDA Guidance for Industry "Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines." These differences include the use of point estimates in the CPMP Guidance and lower limits of 95% confidence intervals in the FDA Guidance, the definition of elderly (≥ 61 years in the CPMP Guidance and ≥ 65 in the FDA Guidance), the use of GMR in the CPMP Guidance only, and the need to meet the criteria for all three strains (FDA Guidance) compared to any one strain (CPMP).

Results of Study V58P2

This study was conducted in a single center at the Princess Margaret Hospital in Christchurch, New Zealand. The first subject was enrolled on March 11, 2003 and follow up for the last study subject was completed on April 23, 2003.

A total of 223 adults were enrolled, randomized, and vaccinated in Study V58P2. All subjects provided Day 1 and Day 222 blood samples for immunogenicity. All provided safety data for the entire study period.

Study demographics are shown in the following table.

Table 38: Study V58P2 – Demographics

	18-61 Years of Age		**≥ 61 Years of Age**	
	Cell derived	**Agriflu**	**Cell derived**	**Agriflu**
Mean Age (in years)	47.2	46.7	68.8	70.5
% Female	52%	58%	48%	50%
% Caucasian	98%	96%	100%	100%
Percent with previous influenza vaccination	82%	72%	94%	96%

Source: BLA 125297, CSR, text, pages 62-63

Reviewer comment: The majority of subjects were Caucasian. The remaining race / ethnicity data were not provided. Most subjects had previously been vaccinated. This may have affected baseline antibody levels and immunogenicity results.

The immunogenicity results for both age groups are shown in the table below.

Table 39: Study V58P2 – Point Estimates (Lower Bound 95% Confidence Interval) for HI Titers in Subjects by Age Cohort

	18-60 Years of Age		**≥61 Years of Age**	
Influenza Strain	**Cell-Derived Vaccine**	**Agriflu (Egg Based)**	**Cell-Derived Vaccine**	**Agriflu (Egg Based)**
Pre-Vaccination % of Subjects with HI Titers≥1:40				
H1N1	52% (38%)	40% (28%)	69% (54%)	57% (43%)
H3N2	71% (58%)	81% (68%)	76% (62%)	82% (70%)
B	5% (1%)	2% (0.4%)	4% (0%)	4% (0%)
Seroconversion Rate				
H1N1	25% (14%)	37% (24%)	9% (3%)	13% (5%)
H3N2	39% (26%)	30% (18%)	30% (18%)	13% (5%)
B	38% (25%)	28% (17%)	37% (24%)	30% (19%)
% of Subjects with HI Titers≥1:40 Post-Vaccination				
H1N1	77% (64%)	79% (66%)	81% (69%)	75% (62%)
H3N2	95% (85%)	96% (88%)	94% (85%)	93% (83%)
B	46% (33%)	39% (26%)	43% (29%)	38% (25%)
GMR				
H1N1	2.39 (1.63)	4.41 (3.01)	1.59 (1.3)	1.69 (1.39)
H3N2	3.38 (2.42)	2.5 (1.8)	2.62 (1.95)	1.66 (1.24)
B	3.01 (2.28)	2.92 (2.22)	2.96 (2.21)	2.76 (2.07)

Source: BLA 125297, CSR, Tables 11.4.1.1-1 – 14.1.1.-3 and 11.4.1.2-1 – 1.4.1.2-3 pages 69-84

The results of Study V58P2 met the CPMP criteria for successfully demonstrating immunogenicity to each of the three influenza strains in each age cohort.

> *Reviewer comment:* This study was designed to meet the CPMP criteria, and the results of the study demonstrated immunogenicity based on this criteria. However, as discussed previously in this review, CBER criteria are more stringent; and the results of Agriflu did not meet the criteria set forth in the FDA Guidance. Using the FDA criteria, the seroconversion results did not meet the criteria set forth in the Guidance for any of the three strains in either of the two age groups. The percentage of subjects with post-vaccination titers ≥ 1:40 met the criteria for the A/H3N2 strain only in the 18 to 60 year age group cohort. In the CBER Guidance, the elderly population is defined as 65 years of age and older, so the age breakdown used in this study may allow for some bias in favor of Agriflu if CBER criteria for 65 years and older are used to measure the result in subjects 61 years of age and up. When using CBER criteria for the older age group in this study, the criteria were met for both influenza A strains but not the B strain. In summary, the results of this study would not satisfy CBER criteria for immunogenicity.

At baseline, the percentage of subjects with HI titers of ≥ 1:40 was highest for the influenza A/H3N2 strain and lowest for the B strain. The applicant reanalyzed data to examine the results

in subjects with HI titers < 1:40 at baseline and in subjects with HI titers ≥ 1:40 at baseline separately. In the subpopulation with low antibody titers at baseline, the CBER criteria for percentage of subjects with post-vaccination titers ≥ 1:40 and for seroconversion were not met for any strain in either age cohort. In the subgroup with higher antibody titers at baseline, the criteria for seroconversion were not met for any influenza antigen or for either age cohort. The criteria were met for the percentage of subjects with post-vaccination HI titers ≥ 1:40 for both influenza A strains in both age cohorts but not for influenza B in either age cohort.

> *Reviewer comment:* The applicant performed a subgroup analysis to determine if baseline antibody levels influenced study results. It does not appear that low or high baseline antibody titers were related to the immunogenicity results. CBER criteria for seroconversion would not have been met for any influenza strain.

The applicant also provided the results of a subgroup analysis based on positive or negative history of previous influenza vaccination. In 18-60 year old subjects who had not been previously vaccinated, the CBER criteria for seroconversion were met for both influenza A strains and the criteria for percentage of subjects with a post-vaccination titer ≥ 1:40 were met for the influenza A/H3N2 strain only. There were too few subjects who were 61 years of age and older and who had not been previously vaccinated (n=3) for a valid analysis. Of the subjects in both age cohorts who had been previously vaccinated for influenza, the CBER criteria were not met for seroconversion for any influenza strain in either age cohort. The percentage of subjects with post-vaccination titers ≥ 1:40 were met for both influenza A strains in both age cohorts but not for the influenza B strains in either age group.

> *Reviewer comment*: In this analysis, antibody titers were higher in those subjects who had not been previously vaccinated. The rates of seroconversion were higher in subjects who had not been previously vaccinated, but overall the percentage of subjects with post-vaccination titers ≥ 1:40 was similar regardless of vaccine history. The antibody response to influenza B was poor in both analyses. While this analysis is of interest, influenza vaccines are not provided based on vaccine history, so the results are not relevant to use of influenza vaccine outside of a clinical trial setting.

Safety data were provided and will be discussed briefly. The overall incidence of solicited adverse reactions by vaccine and by age group is shown in the table below.

Table 40: Study V58P2 – Percentage of Subjects with Solicited Adverse Reactions by Age and Vaccine Arm

	18-60 Years of Age		≥61 Years of Age	
Type of Solicited Adverse Reaction	**Cell-Derived Vaccine**	**Agriflu (Egg Based)**	**Cell-Derived Vaccine**	**Agriflu (Egg Based)**
Any	67%	70%	44%	34%
Local	57%	53%	28%	25%
Systemic	38%	42%	22%	20%

Source: BLA 125297, CSR, text, page 160

Reviewer comment: The percentage of subjects with any solicited AE, solicited local AEs, or solicited systemic AEs was lower in the older age cohort; this is typically observed with influenza vaccines and is likely due to immunosenescence. The percentage of subjects with solicited AEs was similar between the two vaccine arms except for the overall rate in subjects 61 years of age and older. This increase does not appear to be related to either a specific local or systemic solicited AEs since the percentage of subjects 61 years of age and older is similar for local and for systemic adverse reactions.

The percentage of subjects with individual solicited local adverse reactions is shown in the table below.

Table 41: Study V58P2 – Percentage of Subjects with Individual Local Solicited Adverse Reactions by Age and Vaccine Arm

	18-60 Years of Age		≥61 Years of Age	
	Cell-Derived Vaccine	**Agriflu (Egg Based)**	**Cell-Derived Vaccine**	**Agriflu (Egg Based)**
Pain	52%	44%	17%	16%
Erythema	25%	30%	6%	7%
Induration	23%	28%	7%	7%
Swelling	13%	25%	4%	5%
Ecchymosis	16%	9%	11%	4%

Source: BLA 125297, CSR, Table 12.2.3.1-1, page 162

Reviewer comment: Pain was the most frequently reported local solicited AE in both age cohorts. Pain, erythema, induration, and swelling were all reported in one-fourth or more of Agriflu recipients in the 18 to 60 year old age cohort. Overall, the rates of individual local solicited AEs were similar between the two arms, and the only AE with more than 10% difference between arms was swelling in the 18-60 year age cohort.

Individual solicited systemic adverse reactions are shown in the table below.

Table 42: Study V58P2 – Percentage of Subjects with Individual Systemic Solicited Adverse Reactions by Age and Vaccine Arm

	18-60 Years of Age		≥61 Years of Age	
	Cell-Derived Vaccine	**Agriflu (Egg Based)**	**Cell-Derived Vaccine**	**Agriflu (Egg Based)**
Headache	25%	23%	11%	11%
Fatigue	14%	16%	7%	4%
Malaise	5%	18%	11%	9%
Sweating	7%	11%	6%	4%
Myalgia	5%	11%	2%	4%
Arthralgia	5%	5%	2%	2%
Chills	2%	4%	4%	2%
Fever	0	0	0	2%

Source: BLA 125297, CSR, Table 12.2.3.1-1, page 162

Reviewer comment: Headache was the most frequently reported solicited systemic adverse reaction in both age cohorts. Fatigue, malaise, sweating, and myalgia were also reported in more than 10% of Agriflu recipients in the 18-60 year age cohort. In the 18-60 year old cohort, solicited systemic reactions were generally more common in the Agriflu arm than in the cell-derived vaccine cohort. Solicited adverse events were less common in the older age cohort, and headache was the only solicited AE reported in more than 10% of Agriflu recipients in this cohort.

Unsolicited adverse events were reported in 25% of cell-derived vaccine recipients and 28% of Agriflu recipients in the 18-60 year age cohort and in 15% of cell-derived vaccine recipients and 30% of Agriflu recipients in the elderly cohort. The only unsolicited adverse events reported in more than two Agriflu recipient in the 18 to 60 year old age group were upper respiratory tract infection (n=4 or 7%) and pharyngitis (n=3 or 5%). There were no unsolicited AEs reported in more than two elderly Agriflu recipients.

Reviewer comment: The percentage of elderly subjects with unsolicited AEs was substantially higher in the Agriflu arm than in the cell-derived vaccine arm. There was no increase in the percentage of Agriflu recipients with any individual adverse event or class of AEs. The reason for this difference is unclear.

There were no serious AEs, AEs leading to study discontinuation, or deaths in this study.

In conclusion, immunogenicity was demonstrated in this study by CPMP standards but not by CBER standards. However, the study was designed to use the CPMP criteria and not the CBER criteria and the sample size was relatively small resulting in large confidence intervals that

affected CBER criteria but not CPMP criteria. There were no safety signals or concerns noted in this study. Safety results were consistent with other studies of Agriflu.

Study V58P4

A Phase 3, observer-blind, randomized, multi-center study to evaluate safety, tolerability, and immunogenicity of a single intramuscular dose of trivalent subunit influenza vaccine produced in mammalian cell culture and a trivalent subunit influenza vaccine produced in embryonated hen eggs, in healthy adult and elderly subjects

Study Design

The study design of V58P4 was almost identical to that of Study V58P2 with the following exceptions.

- In V58P4, a second immunogenicity objective was added to demonstrate the non-inferiority of the cell-derived vaccine to Agriflu. The criteria for demonstrating non-inferiority were 1) the lower limit of the 95% CI for the percentage of subjects with HI titers ≥ 1:40 post-vaccination was > -10%, 2) the lower limit of the 95% CI for the percentage of subjects with seroconversion was > -10%, and 3) the lower limit of the 95% CI for the GMR ratio was > 0.5.
- A larger sample size was planned for V58P4; sample size was based on the non-inferiority analysis.
- Each vaccine dose contained the antigens recommended for the 2004-2005 influenza season in the Northern Hemisphere:
    - A/New Caledonia/20/99 H1N1-like, 15 µg,
    - A/Wyoming/3/2003 H3N2-like, 15 µg, and
    - B/Jiangsu/10/2003-like, 15 µg.

Please see the description of Study V58P2 above for additional information on the study design for V58P4.

Study Results

Study V58P4 was conducted at five study centers in Poland. The first subject was enrolled on September 14, 2004, and the last subject completed the study on May 16, 2005.

A total of 2654 adult volunteers were enrolled and vaccinated in the study: 1300 in the 18-60 year old age cohort and 1354 in the 61 years and older cohort. Forty-five subjects withdrew from the study prematurely: 24 in the 18-60 year old cohort and 21 in the 61 years and older age cohort. The percentage of subjects who withdrew was similar in the cell-derived vaccine arm (2% of subjects in each age cohort) and in the Agriflu arm (2% of adults 18-60 years of age and 1% of those 61 years of age or older). Five subjects in the 18-60 year age group and four in the elderly age group withdrew prior to having the post-vaccination blood draw. All but four premature study discontinuations were due to loss to follow-up or withdrawal of consent. The

four other subjects were discontinued prematurely because of three deaths in the elderly population and inappropriate enrollment of one subject with hepatic cirrhosis and hepatitis B.

Major protocol violations that resulted in subjects being excluded from the Per Protocol population were reported for six subjects in the 18-60 year old cohort and eight in the 61 years of age and older cohort. In the younger adult cohort, one subject had the second blood draw outside the pre-specified time window (cell-derived vaccine arm) and five withdrew before the second blood draw (one in cell-derived arm and four in the Agriflu arm). In the elderly population, three subjects, all in the cell-derived vaccine arm, had the second blood draw outside of the study window, one subject in the cell-derived arm did not meet the entry criteria, and four subjects (two in each arm) withdrew before the second blood draw.

> *Reviewer comment:* The number of premature study discontinuations and major protocol violations were relatively small suggesting that the study was well conducted. The number of premature discontinuations and of protocol violations was similar between the two vaccine groups.

Study demographics are shown in the table below

Table 43: Study V58P4 – Demographics

	18-61 Years of Age		**≥ 61 Years of Age**	
	Cell derived N=652	**Agriflu N=648**	**Cell derived N=678**	**Agriflu N=676**
Mean Age (in years)	38.7	38.3	69.1	68.8
% Female	58%	57%	57%	55%
% Caucasian	100%	100%	100%	100%
Percent with previous influenza vaccination	38%	42%	59%	59%

Source: BLA 125297, CSR, Tables 11.2.1-1 and 11.2.1-2 and text, pages 75-76

> *Reviewer comment*: The baseline characteristics were similar in the two vaccine arms. The race and ethnicity in this study does not reflect the racial and ethnic diversity of the U.S. population; however, there are no known differences in antibody response to influenza by race or ethnicity.

The immunogenicity results for both age groups are shown in the table below.

Table 44: Study V58P4 – Point Estimates (Lower Bound 95% Confidence Interval) for HI Titers in Subjects by Age Cohort

	18-60 Years of Age		**≥61 Years of Age**	
Influenza Strain	**Cell-Derived Vaccine N=650**	**Agriflu (Egg Based) N=644**	**Cell-Derived Vaccine N=672**	**Agriflu (Egg Based) N=674**
Pre-Vaccination % of Subjects with HI Titers≥1:40				
H1N1	29% (26%)	33% (29%)	30% (27%)	31% (27%)
H3N2	65% (61%)	63% (60%)	66% (63%)	59% (56%)
B	16% (13%)	18% (15%)	23% (20%)	20% (17%)
Seroconversion Rate				
H1N1	69% (65%)	67% (63%)	55% (51%)	55% (51%)
H3N2	63% (59%)	64% (60%)	68% (65%)	65% (61%)
B	85% (82%)	81% (78%)	80% (77%)	73% (70%)
Post-Vaccination % of Subjects with HI Titers≥1:40				
H1N1	92% (89%)	92% (89%)	85% (82%)	85% (82%)
H3N2	99% (98%)	99% (98%)	97% (96%)	98% (97%)
B	90% (88%)	91% (88%)	90% (88%)	89% (87%)
GMR				
H1N1	11 (10)	11 (9.34)	5.74 (5.15)	5.96 (5.35)
H3N2	5.99 (5.37)	7.08 (6.34)	7.25 (6.47)	8.36 (7.46)
B	13 (12)	12 (11)	12 (11)	9.25 (8.42)

Source: BLA 125297, CSR, Tables 11.4.1.1-1 – 14.1.1.-3 and 11.4.1.2-1 – 1.4.1.2-3 pages 80-85

Reviewer comment: The percentage of subjects with HI titers of 1:40 or greater post-vaccination, and the percentage of subjects with seroconversion met the CBER criteria for all three strains, for both vaccines, and for both age cohorts. The results between vaccine arms were similar.

It is unclear why these results differ from those in Study V58P2 given the similarities in both study design and subject demographics. The percentage of subjects with previous influenza vaccination was lower in V58P4 compared to V58P2, and it is possible that the results are related to pre-existing immunity in V58P2. However, in Study V58P2 the results of previously vaccinated subjects and previous unvaccinated subjects were similar. It is also possible that the results for the two studies vary because of the difference in immunogenicity in the vaccine influenza A/H3N2 and B strains of the vaccines used in the studies.

The cell-derived vaccine was demonstrated to be non-inferior to Agriflu for all three strains and in both age cohorts.

The results were also provided for subjects with baseline HI titers less than 1:40. In this secondary analysis, CBER criteria were met for both seroconversion rate and percentage of subjects with post-vaccination HI titers ≥ 1:40 for all three strains, for both vaccine arms, and for both age cohorts.

Safety data were analyzed for the 2654 subjects who were vaccinated in the study. The overall incidence of solicited adverse reactions by vaccine and by age group is shown in the table below.

Table 45: Study V58P4 – Percentage of Subjects with Solicited Adverse Reactions by Age and Vaccine Arm

	18-60 Years of Age		**≥61 Years of Age**	
Type of Solicited Adverse Reaction	**Cell-Derived Vaccine N=652**	**Agriflu (Egg Based) N=648**	**Cell-Derived Vaccine N=678**	**Agriflu (Egg Based) N=676**
Any	40%	41%	34%	32%
Local	32%	31%	22%	18%
Systemic	22%	23%	22%	22%

Source: BLA 125297, CSR, Tables 12.2.1.1-1 and 12.2.1.2-1, pages 108 and 110

Reviewer comment: There were fewer reactogenicity adverse reactions in the elderly age group compared to cohort of adults 18 to 60 years of age. The percentage of subjects with solicited AEs was similar between the two vaccine arms.

The percentage of subjects with individual solicited local adverse reactions is shown in the table below.

Table 46: Study V58P4 – Percentage of Subjects with Individual Local Solicited Adverse Reactions by Age and Vaccine Arm

	18-60 Years of Age		**≥61 Years of Age**	
	Cell-Derived Vaccine	**Agriflu (Egg Based)**	**Cell-Derived Vaccine**	**Agriflu (Egg Based)**
Pain	22%	17%	9%	5%
Erythema	14%	16%	11%	11%
Induration	6%	6%	5%	4%
Swelling	4%	4%	3%	3%
Ecchymosis	3%	3%	4%	4%

Source: BLA 125297, CSR, Tables 12.2.3.1-1 and 12.2.3.2-1, pages 114 and 121

Pain was the most commonly reported solicited local adverse reaction in subjects 18 to 60 years of age and the second most common in the elderly cohort of subjects. The majority of solicited local AEs were mild or moderate in intensity. Severe local reactions were reported in five adults

between 18 and 60 years of age who received Agriflu (two severe pain AEs and one severe AE each of ecchymosis, erythema, and swelling) and in one elderly Agriflu recipient (erythema).

> *Reviewer comment*: Pain and erythema were reported in more than 10% of Agriflu recipients in the 18 to 60 year old age cohort. Erythema was the most frequently reported solicited local AE in elderly Agriflu recipients and the only solicited local AE reported in more than 10% of elderly subjects. The rates of individual local solicited AEs were similar between the two arms.

Individual solicited systemic adverse reactions are shown in the table below.

Table 47: Study V58P4 – Percentage of Subjects with Individual Systemic Solicited Adverse Reactions by Age and Vaccine Arm

	18-60 Years of Age		**≥61 Years of Age**	
	Cell-Derived Vaccine	**Agriflu (Egg Based)**	**Cell-Derived Vaccine**	**Agriflu (Egg Based)**
Headache	12%	12%	10%	10%
Fatigue	11%	11%	11%	12%
Malaise	11%	11%	10%	11%
Myalgia	7%	8%	7%	8%
Arthralgia	5%	4%	6%	7%
Chills	4%	4%	3%	4%
Sweating	4%	4%	6%	7%
Fever	<1%	1%	1%	1%

Source: BLA 125297, CSR, Table 12.2.3.1-1, page 162

Headache was the most commonly reported solicited systemic adverse reaction in the 18-60 year age group, while fatigue was the most frequently reported solicited systemic AE in the elderly age group. Headache, fatigue, and malaise were the solicited systemic AEs reported in more than 10% of subjects in any vaccine arm or age group. Fever was uncommon and was reported in 1% or fewer of study subjects. Severe solicited AEs were uncommon. Severe solicited systemic AEs were reported in two or more Agriflu recipients for malaise (n=4), headache (n=3), and fatigue (n=3) in the 18-60 year old cohort. In the elderly cohort, severe solicited systemic AEs were reported in two or more Agriflu recipients for headache (n=5), sweating (n=4), malaise (n=3), myalgia (n=3), arthralgia (n=3), fatigue (n=3), and chills (n=2). No subjects had severe fever (≥40º C).

In both vaccine arms, 2% of adults 18 to 60 years of age stayed at home due to a solicited adverse reaction. Six percent of Agriflu recipients and 7% of cell-derived vaccine recipients used analgesics or antipyretics because of a solicited adverse event. In the elderly population, 2% of Agriflu recipients and 3% of cell-derived vaccine recipients stayed home due to solicited

adverse reactions, and 4% of Agriflu recipients and 5% of cell-derived vaccine recipients used analgesics / antipyretics because of solicited adverse reactions.

> *Reviewer comment*: The incidence and types of individual solicited systemic adverse events were similar between the two vaccine arms. Headache, fatigue, and malaise were the most common solicited systemic AEs and were all reported in more than 10% of subjects. The findings were consistent with other studies of Agriflu.

Unsolicited adverse events were reported in 15% of cell-derived vaccine recipients and 14% of Agriflu recipients in the 18-60 year age cohort and in 15% of cell-derived vaccine recipients and 13% of Agriflu recipients in the elderly cohort. The organ system with the highest number of unsolicited AEs was infections and infestations (6% of cell-derived vaccine recipients and 7% of Agriflu recipients in 18-60 year age group and 4% of cell-derived vaccine recipients and 5% of Agriflu recipients in elderly age group). There was no other organ system in either age group or either arm in which unsolicited AEs were reported in 5% or more subjects. The most common individual unsolicited AEs were reported in the Clinical Study Report for those AEs judged to be vaccine-related only. Vaccine-related AEs that were reported in 1% or more of subjects in either study arm and in subjects 18-60 years of age were rhinitis (1% of each vaccine arm), pharyngeal pain (1% of each arm), and ecchymosis (<1% of cell-derived recipients and 1% of Agriflu recipients).

Severe unsolicited AEs were reported in 5 subjects from 18 to 60 years of age. This included two cell-derived recipients (diarrhea and laryngitis) and three Agriflu recipients (toothache, otitis media, and headache). There were seven elderly cell-derived vaccine recipients who reported severe unsolicited AEs: acute myocardial infarction, coronary artery disease, retinal detachment, carbon monoxide poisoning, esophageal neoplasm, lung squamous cell carcinoma, and procedural complication. Twelve severe unsolicited AEs were reported in six elderly Agriflu recipients: angina, atrial fibrillation, vertigo, vomiting, rhinitis, gallbladder cancer, lung adenocarcinoma, cerebrovascular accident, headache, cough, pharyngolaryngeal pain, and hypertensive crisis. None of the severe events were judged as related to study vaccine.

There were 12 serious AEs in the 18-60 year age group: seven in the cell-derived vaccine arm and five in the control arm. One SAE occurred within the 25 days of vaccination: a case of alcohol poisoning. The other serious AEs reported in this age group were hypoacusis, post-operative hernia, MI, bronchopneumonia, and COPD in the Agriflu arm and nephrolithiasis, hypoacusis (two reports), alcohol poisoning, inguinal hernia, atrial fibrillation, and bronchopneumonia in the cell-derived vaccine arm. Thirty-four elderly subjects (18 in the cell-derived vaccine arm and 16 in the Agriflu arm) had serious AEs. SAEs reported in the first 25 days post-vaccination were atrial fibrillation on Day 6 in a cell-derived vaccine recipient and inner ear disorder in an Agriflu recipient. All SAEs reported in the elderly population are listed in the table below; some subjects had more than one SAE.

Table 48: Study V58P4 – Serious Adverse Events Reported in Subjects ≥ 61 Years of Age

Cell-Derived Vaccine		**Agriflu**	
SAE	**# of Events**	**SAE**	**# of Events**
Atrial fibrillation	4	Angina	3
Myocardial infarction	2	Atrial fibrillation	2
Coronary artery disease	2	Osteoarthritis	2
Pneumonia	2	Pneumonia	2
Syncope, vasovagal	2	Myocardial ischemia	1
Myocardial ischemia	1	Lung neoplasm	1
Lung neoplasm	1	Gall bladder cancer	1
Esophageal neoplasm	1	Hypertension	1
Dyspepsia	1	Atherosclerosis	1
Food poisoning	1	Colitis	1
Gastric hemorrhage	1	Diverticulum	1
Sleep apnea	1	Acute pancreatitis	1
Pulmonary embolism	1	Carpal tunnel syndrome	1
Procedural complication	1	Inner ear disorder	1
Tibia fracture	1	Cholecystitis	1
Uterine Polyp	1	---	---
Retinal detachment	1	---	---
Glaucoma	1	---	---

Source: BLA 125297, CSR, Table 12.3.1.2-2, pages 133-135

Reviewer comment: There were more SAEs in the elderly population than in the younger population; however, the majority of SAEs reported in the elderly were consistent with illnesses that are common to an elderly population. There were slightly more cardiac events reported in recipients of the cell-derived vaccine than in Agriflu recipients, but the numbers are small, the cardiac diseases varied, and the onset of the majority of these SAEs was more than 25 days after vaccination. Therefore, this difference was likely due to chance.

In the 18 to 60 year age group, there were no deaths on study and no AEs leading to study discontinuation. The three elderly subjects who died were the only subjects who discontinued the study prematurely due to an adverse event. One Agriflu recipient died 166 days after vaccination due to lung adenocarcinoma. Another Agriflu recipient died due to a cerebral vascular accident, which occurred 39 days post-vaccination. A cell-derived vaccine recipient died of carbon monoxide poisoning on Study Day 25.

Reviewer comment: In the opinion of this reviewer, it is unlikely that any of these deaths were vaccine-related.

In conclusion, the immunogenicity results of this study successfully met the immunogenicity criteria outlined in the FDA Guidance for Industry, "Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines." These criteria were met for all three vaccine influenza strains, in both vaccine arms, and in both age cohorts. The incidence and types of adverse events reported in this study were consistent with other studies of Agriflu, and no new safety signal was identified.

Study V58P9

A Phase 3 randomized, controlled, observer-blind, multi-center study to evaluate safety, tolerability, and immunogenicity of a single intramuscular dose of three lots of trivalent subunit influenza vaccine produced in mammalian cell culture or of a trivalent subunit influenza vaccine produced in embryonated hen eggs in healthy adult subjects aged 18 to <61 years

Study Design

The immunogenicity objective of this study was to evaluate immunogenicity of the two study vaccines and of each vaccine lot three weeks after a single 0.5 mL intramuscular injection in accordance with the requirements of the current European Union recommendations (CPMP/BWP/214/96). The safety objective was to evaluate the safety and tolerability of three lots of the cell-derived influenza subunit vaccine as compared to a conventional egg-derived vaccine (Agriflu) for the three weeks post-vaccination.

This was a Phase 3, randomized, controlled, observer-blind study of the safety and immunogenicity of a cell-derived influenza vaccine. A total of 1199 healthy adult volunteers were randomized in a 2:2:2:1 ratio to receive either one of three lots of the cell-derived vaccine or Agriflu. The vaccine was administered intramuscularly as a 0.5 mL dose in the deltoid muscle, preferably of the non-dominant arm. Antibody response was measured pre-vaccination, and at Days 22 and 181 post-vaccination. Immunogenicity data through Day 22 and safety data through the six month follow-up were included in this submission.

> *Reviewer comment*: On October 17, 2007, the applicant notified CBER of a pipettor malfunction that affected this study. As a result of this pippetor error, there was an underestimate of liquid volume in the HI assays of approximately 20-25%. CBER asked Novartis to repeat the HI assays on saved sera. At this time, the applicant has repeated the HI assays for the Days 1 and 22 time points but not the Day 181 time point. Therefore, the immunogenicity data were provided for Days 1 and 22 and the safety data were provided for the entire study period.

A subset of subjects was followed for influenza-like illnesses (ILIs) from Day 22 until the end of the 180 study period. ILI was defined as the sudden onset of fever (axillary temperature ≥38º C) plus at least one systemic symptom such as myalgia, arthralgia, osteoalgia, tiredness, weakness, headache, ear ache, eye complaints, or chills; and at least one respiratory symptom such as sore throat, cough, hoarseness, wheezing, runny nose, or nasal congestion. Episodes of ILI were captured by active surveillance (telephone calls every 10 days at the time of a local influenza outbreak) and by passive surveillance (subjects were instructed to immediately contact the

investigator within 48 hours of symptom onset). Once an ILI was identified, the study personnel were to visit the subject at home and confirm the symptoms, perform a brief physical examination, and obtain nasopharyngeal swabs for virus isolation and identification.

> *Reviewer comment*: The study was not designed or powered to explore an objective for clinical endpoints. These results were not provided in the clinical Study Report.

Each vaccine dose contained the antigens recommended for the 2005-2006 influenza season in the Northern Hemisphere:

A/New Caledonia/20/99 H1N1-like, 15 µg,
A/California/7/2004 H3N2-like, 15 µg, and
B/Shanghai/361/2002-like, 15 µg.

Subjects were seen in clinic on Days 1, 22, and 181. On Day 1, subjects received a single 0.5 mL dose of study vaccine in the deltoid muscle, preferably in the non-dominant arm. Anti-HI antibody titers were collected prior to vaccination on Day 1 and again on Days 22 and 181. Local and systemic reactogenicity events occurring on the day of vaccination (from six hours post-vaccination) and during the six days post-vaccination were recorded on a diary card. Information on unsolicited adverse events (AEs) was collected from Days 1 to 22. Information on serious AEs and AEs requiring a physician's visit and / or resulting in premature study discontinuation was collected throughout the entire 180 day study period.

Adult subjects who were from 18 to 60 years of age and in good health were enrolled in Study V58P9. Individuals were excluded from study participation if they had received an influenza vaccine or had laboratory-confirmed influenza in the previous six months. Individuals were also excluded for acute illness, history of hypersensitivity to any component of the study vaccine, history of serious vaccine reactions or allergy to any vaccine component, and for any impairment of the immune system.

Immunogenicity was determined by hemagglutination inhibition titers and evaluated using CHMP criteria for seroconversion, for geometric mean ratio, and for percentage of subjects with HI titers of 1:40 or more post-vaccination. Seroconversion was defined as a pre-vaccination HI titer of <1:10 with a post-vaccination titer ≥ 1:40 *or* as at least a four fold increase in HI titer from Day 1 to Day 22. The geometric mean ration (GMR) was the ratio of the GMT at day 22 to the GMT on Day 1.

Subjects were seen in clinic three times: on Days 1, 22, and 180. A subset of subjects who were being following for development of an ILI were visited at home if they developed signs and symptoms of an ILI. A medical history, physical examination, and vital signs were obtained at the Day 1 study visit. The physical examination was repeated at the Days 22 and 180 visits.

Subjects received the study vaccine on Day 1 and were observed for at least 30 minutes after vaccination. Information on reactogenicity adverse events was collected on the day of vaccine administration, starting six hours after vaccination, and for the subsequent six days.

- Information was collected on the following local reactogenicity events: ecchymosis, erythema, induration, swelling, and pain at the injection site. The severity of local reactions, except pain, will be categorized as none, 1 to ≤10 mm, 11 to ≤25 mm, 51 to ≤100 mm, and >100 mm.
- Information on the following systemic reactogenicity events was collected: chills, malaise, myalgia, arthralgia, headache, sweating, fatigue, and fever. The severity of pain and systemic reactogenicity events was categorized as none, mild (transient and no limitation on normal daily activity), moderate (some limitation in normal daily activity), and severe (unable to perform normal daily activity). Subjects recorded their daily axillary temperature on the diary card for 7 days. Fever was defined as an axillary temperature ≥38ºC with severe fever defined as ≥40ºC.
- Additional information collected in the diary cards was the impact on daily life as measured by number of days that the subject stayed at home due to an adverse reaction and the use of analgesic / antipyretic medication.

Information on all other adverse events (unsolicited AEs) was collected for the first 22 days of the study. No safety laboratory testing was performed.

Study V58P9 was an observer-blind study. Designated unblinded study personnel were responsible for administration of the study vaccines and for vaccine accountability. These personnel were not involved in trial conduct or monitoring and did not have access to the CRF.

Subjects were randomized using a list generated by Chiron Biostatistics and Clinical Data Management Department; subjects were randomized in a 2:2:2:1 ratio to one of three lots of the cell-derived vaccine or to Agriflu.

Safety was evaluated by information on adverse events, including solicited reactogenicity adverse events. Statistical analyses of these AEs were descriptive.

Lot-to-lot consistency was measured by the pair wise comparison of each of the ratio of post-vaccination GMTs between the three lots. Bioequivalence would be achieved if the ratios for these comparisons were between 0.5 and 2.0.

> *Reviewer comment*: According to the FDA Guidance for Industry, "Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines," lot-to-lot consistency is achieved if the two-sided 95% CIs on ratios of GMTs are 1.5. This criterion is stricter than the criterion used in this study.

Endpoints used as measures of immunogenicity included the percentage of subjects achieving seroconversion at Day 22, percentage of subjects with HI titer ≥ 1:40 at Day 1 and Day 22, GMTs at Day 1 and Day 22, and the Day 22/Day 1 geometric mean ratio.

The percentage of subjects with HI titers of 1:40 or higher post-vaccination, the percentage of subjects with seroconversion, and the GMR were evaluated using the CPMP Note for Guidance on Harmonisation of Requirements for Influenza Vaccines (CPMP/BWP/214/96). The CPMP standards for adults 18 to less than 60 years of age include the point estimates for:

- the percentage of subjects with seroconversion or significant increase in HI antibody titer should meet or exceed 40%
- the percentage of subjects achieving an HI antibody titer ≥1:40 post-vaccination should meet or exceed 70%, and
- the geometric mean increase in antibody titer should be greater than 2.5.

Reviewer comment: The criteria recommend in the CPMP Note for Guidance of Harmonisation of Requirements for Influenza Vaccines differ slightly from those recommended in the FDA Guidance for Industry "Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines." Differences include the use of point estimates in the CPMP Guidance and lower limits of 95% confidence intervals in the FDA Guidance, the use of GMR in the CPMP Guidance only, and the need to meet the criteria for all three strains (FDA Guidance) compared any one strain (CPMP Note).

Study Results

Study V58P9 was conducted at two study centers in Vilnius and Panevezys, Lithuania. The first study subject was enrolled on September 19, 2005; the last subject completed the study on April 18, 2006. A total of 1199 subjects were randomized and vaccinated: 1028 in the cell-derived vaccine arms and 171 in the Agriflu arm.

Thirty-four subjects discontinued the study prematurely (31 in the cell-derived vaccine arms and three in the Agriflu arm). Five subjects in the cell-derived vaccine arms discontinued before the study before the second visit and therefore, did not have post-vaccination antibody titers obtained. No subjects in the Agriflu arm discontinued before the Day 22 visit. Twenty-nine subjects (26 in the cell-derived vaccine arms and 3 in the Agriflu arm) withdrew before completing the study and did not complete the entire safety follow-up. The reasons for all premature discontinuations (n=31) in the cell-derived vaccine arms were loss to follow-up (25), consent withdrawn (5), and death (1). All three premature study discontinuations in the Agriflu arm were due to loss to follow-up.

There were a total of 158 protocol deviations in 105 subjects. The majority of subjects with protocol violations (101) were enrolled at the Vilnius site. The most common reasons for protocol violations were received excluded medication (47 subjects in cell-derived vaccine arms and 6 in Agriflu arm), third blood draw not performed (31 subjects in cell-derived vaccine arms and 3 in Agriflu arm), consent withdrawn on Day 22 or later in study (23 subjects in cell-derived vaccine arms and 3 in Agriflu arm), and third blood draw outside of window (14 subjects in cell-derived vaccine arms and 2 in Agriflu arm). Of these subjects, 15 subjects were excluded from the Per Protocol population: 8 did not meet entry criteria due to active tuberculosis disease (6 in

cell-derived vaccine arms and 2 in Agriflu arm), 5 in the cell-derived vaccine arm due to no Day 22 blood draw, and two subjects who were vaccinated with the wrong vaccine (one subject randomized to cell-derived vaccine received Agriflu and one subject randomized to Agriflu received the cell-derived vaccine).

> *Reviewer comment*: The reasons for premature study discontinuations and the percentage of subjects with study discontinuations were similar between the two study vaccines. The types and percentages of protocol violations were also similar between the two study arms. It is notable that the overwhelming majority of protocol violations were from one of the two sites. It is unclear if reporting of protocol violations varied between sites or if study conduct varied between the two sites. The study results will be examined for other differences between the two study sites.

The demographics and baseline characteristics of the study population are shown in the table below. The results for the three lots of the cell-derived vaccine are combined.

Table 49: Study V58P9 – Demographics

	Cell Derived N=1017	**Agriflu N=168**
Mean Age (in years)	32.5	32.4
% Female	61%	64%
% Caucasian	100%	100%
Percent with previous influenza vaccination	23%	26%

Source: BLA 125297, Table 11.2-1, page 69

> *Reviewer comment*: As shown in the table above, the demographics and baseline characteristics were similar between the two vaccine groups. The study was conducted in Lithuania and enrolled a Caucasian population. Although this population does not represent the racial and ethnic diversity found in the United Sates, there is no known difference in antibody response to influenza vaccine by race or ethnicity.

Immunogenicity data are provided in the following table. Because the three lots were shown to be bioequivalent, the results for the three lots are combined.

Table 50: Study V58P9 – Point Estimates (Lower Bound 95% Confidence Interval) for HI Titers

Influenza Strain	Cell-Derived Vaccine N=1017	Agriflu (Egg Based) N=168
Pre-Vaccination % of Subjects with HI Titers≥1:40		
H1N1	29% (26%)	30% (24%)
H3N2	24% (22%)	27% (20%)
B	23% (20%)	21% (15%)
Seroconversion Rate		
H1N1	81% (79%)	77% (70%)
H3N2	83% (80%)	88% (82%)
B	78% (76%)	70% (63%)
Post-Vaccination % of Subjects with HI Titers≥1:40		
SP		
H1N1	94% (92%)	95% (91%)
H3N2	93% (91%)	96% (92%)
B	91% (89%)	88% (82%)
Geometric Mean Ratio		
H1N1	18 (16)	16 (13)
H3N2	14 (13)	17 (14)
B	9.76 (9.04)	8.29 (6.86)

Source: BLA 125297, CSR, Tables 11.4.1-2 – 14.1-4 pages 72-76

The percentage of subjects with HI titers of 1:40 or greater to each of the three influenza strains was similar between the two arms at baseline. The point estimates for seroconversion rate, post-vaccination HI titers greater than 1:40, and the GMR all met the CPMP criteria outlined in the study protocol for successfully demonstrating immunogenicity. The results were similar between the two vaccine groups.

> *Reviewer comment:* The results also met the CBER criteria for successfully demonstrating immunogenicity.

Subjects were stratified by study center. Results for the two study centers are shown in the table below.

Table 51: Study V58P9 – Point Estimates for HI Titers by Study Site

	Site 1		Site 2	
Influenza Strain	**Cell-Derived Vaccine N=589**	**Agriflu (Egg Based) N=98**	**Cell-Derived Vaccine N=428**	**Agriflu (Egg Based) N=70**
Pre-Vaccination % of Subjects with HI Titers≥1:40				
H1N1	36%	38%	19%	20%
H3N2	26%	28%	22%	26%
B	27%	31%	18%	9%
Seroconversion Rate				
H1N1	81%	76%	82%	79%
H3N2	80%	88%	86%	89%
B	80%	70%	76%	70%
Post-Vaccination % of Subjects with HI Titers≥1:40				
H1N1	96%	97%	91%	93%
H3N2	92%	97%	95%	96%
B	93%	93%	87%	80%

Source: BLA 125297, CSR, Tables 11.4.1.1-1 and text, pages 79-81

As shown in the table above, the percentage of subjects with a baseline HI titer of 1:40 or greater to the H1N1 and B strains was higher at Site 1 than at Site 2. The differences at baseline by site appeared to have little effect on the seroconversion rate, which were similar at the two sites. However, the percentage of subjects with post-vaccination titers of 1:40 or greater for the two strains was lower at Site 2.

> *Reviewer comment:* The differences in the percentage of subjects with baseline HI titers ≥ 1:40 at the two study sites may have affected the differences in the percentage of subjects with HI titers ≥ 1:40 post-vaccination. However, the differences were small, and overall, the results between the two sites were similar.

Safety data was analyzed for the 1199 subjects vaccinated. The percentage of subjects with solicited adverse reactions is shown in the table below.

Table 52: Study V58P9 – Percentage of Subjects with Solicited Adverse Reactions

Type of Solicited Adverse Reaction	**Cell-Derived Vaccine N=1028**	**Agriflu (Egg Based) N=171`**
Any	41%	37%
Local	29%	25%
Systemic	25%	23%

Source: BLA 125297, CSR, Tables 12.2.1 -1, page 87

Reviewer comment: The percentage of subjects with solicited adverse reactions was slightly higher in the cell-derived vaccine arm compared to the Agriflu arm. These results are similar to other studies of Agriflu.

The percentage of subjects with individual solicited local adverse reactions is shown in the table below.

Table 53: Study V58P9 – Percentage of Subjects with Individual Local Solicited Adverse Reactions

	Cell-Derived Vaccine	**Agriflu (Egg Based)**
Erythema	20%	18%
Induration	11%	11%
Pain	12%	8%
Swelling	7%	8%
Ecchymosis	4%	6%

Source: BLA 125297, CSR, Tables 12.2.3.1-1, page 94

The most frequently reported local solicited adverse reaction was erythema. Erythema and induration were reported in more than 10% of subjects in both vaccine groups. Pain was reported in more than 10% of subjects in the cell-derived vaccine group but in less than 10% of those in the Agriflu arm. Severe local solicited AEs were uncommon and were reported in less than 2% of subjects in each vaccine group.

Reviewer comment: The percentage of subjects reporting pain was considerably lower than in other studies of Agriflu. The reason for this is unclear.

Individual solicited systemic adverse reactions are shown in the table below.

Table 54: Study V58P9 – Percentage of Subjects with Individual Systemic Solicited Adverse Reactions

	Cell-Derived Vaccine	Agriflu (Egg Based)
Headache	14%	12%
Malaise	13%	12%
Fatigue	13%	11%
Chills	6%	7%
Myalgia	6%	5%
Sweating	4%	3%
Arthralgia	3%	1%
Fever	1%	2%

Source: BLA 125297, CSR, Table 12.2.3.1-1, page 162

Headache, malaise, and fatigue were reported in more than 10% of subjects in both vaccine groups. Fever was uncommon. Severe systemic solicited adverse reactions were uncommon for each individual solicited systemic AE and were reported in less than 1% of each vaccine group.

> *Reviewer comment*: The percentage of individual systemic solicited AEs was similar between the two vaccine groups and was also similar to what has been reported in other studies of Agriflu.

Three percent of subjects in the cell-derived vaccine group and 2% in the Agriflu arm stayed at home due to a solicited adverse reaction. Three percent of subjects in the cell-derived vaccine group and 6% in the Agriflu arm used analgesics / antipyretics for a solicited adverse reaction.

In the 22 days after vaccination, unsolicited adverse events were reported in 10% of subjects who received the cell-derived vaccine and in 9% of those who received Agriflu. Of these, 7% in each vaccine group were judged to be vaccine related. The only individual unsolicited AEs reported in more than 1% of subjects in either vaccine group were rhinitis (2% of subjects who received the cell-derived vaccine and 4% of those who received Agriflu), pharyngolaryngeal pain (2% of subjects in each vaccine group), and erythema (2% of subjects who received the cell-derived vaccine and 1% of those who received Agriflu).

During the entire six month study period, unsolicited AEs were reported in 14% of subjects in the cell-derived vaccine group and in 12% of subjects in the Agriflu arm. AEs were reported most commonly in the infections and infestations system organ class (6% of subjects in both vaccine groups). Unsolicited adverse events were reported in the general and administration site conditions category in 3% of the cell-derived vaccine group and in 1% of subjects in the Agriflu arm; unsolicited AEs in the respiratory, thoracic, and mediastinal disorder category were reported in 2% of the cell-derived vaccine group and in 3% of subjects in the Agriflu arm. Unsolicited adverse events are shown by system organ class in the table below.

Table 55: Study V58P9 – Percentage of Subjects with Unsolicited Adverse Events Reported in >1% of Subjects in Either Vaccine Group by System Organ Class

System Organ Class	Days 1-22		Days 23-181	
	Cell-Derived Vaccine	Agriflu	Cell-Derived Vaccine	Agriflu
Infections and infestations	3%	6%	4%	2%
Respiratory, thoracic, and mediastinal	2%	3%	<1%	0
General disorders and administration site condition	3%	1%	<1%	0
Skin and subcutaneous tissue disorders	2%	2%	<1%	0

Source: BLA 125297, CSR, Table 12.2.3.3-1, page 100

Severe unsolicited adverse events were reported for 6 subjects who received the cell-derived vaccine (diarrhea, fatigue, pyrexia, upper respiratory tract infection, arthralgia, myalgia, headache, and tooth extraction) and for one subject who received Agriflu (menorrhagia).

> *Reviewer comment*: The types of unsolicited adverse events were varied, and there was no increase in either a single type of unsolicited AE or class of AEs.

Serious adverse events were reported in 2% of subjects in both vaccine groups. None were considered to be vaccine related. Of these, only two occurred in the 22 days post-vaccination; both were in the cell-derived vaccine arm. These two were a 22 year old female who was hospitalized for diarrhea seven days post-vaccination and a 21 year old male with a previously planned admission to the hospital eight days post-vaccination. In the period from 3 weeks to 6 months post-vaccination, SAEs were reported in 15 subjects in the cell-derived arm and 3 in the Agriflu arm. Of these SAEs, seven were due to laboratory-confirmed influenza (5 in cell-derived vaccine arm and 2 in Agriflu arm) and were classified as vaccine failures. All seven cases were due to influenza B; further identification of the infecting influenza B strains were not performed, but the influenza B strain circulating in Europe that influenza season differed from the vaccine strain.

There were two pregnancies during this study; both in subjects who received the cell-derived vaccine. Both pregnancies resulted in healthy, full term babies.

There were no premature study discontinuations due to adverse events.

There was one death during the study. This subject died on Day 50 due to suffocation. This adverse event was judged as not related to study vaccine.

Reviewer comment: All but two serious AEs were reported more than three weeks post-vaccination. Neither of the SAEs reported with 22 days of vaccination were judged as vaccine-related. There was a single death in the study; this death does not appear to be related to study vaccine.

In conclusion, the immunogenicity results in Study V58P9 successfully met the criteria outlined in the FDA Guidance for Industry, "Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines." These immunogenicity criteria were met for all three vaccine influenza strains and for both the cell-derived vaccine and Agriflu. In addition, no new safety signals were identified.

8.4 Additional Studies Supporting Safety

The results for 11 additional studies were submitted to support the safety of Agriflu. The safety results for these studies are presented as follows: studies conducted in support of annual registration in Europe (six studies), studies conducted to investigate a thimerosal-reduced formulation of Agriflu (three studies), a single pilot study at a new study site, and a single extension study in which subjects in Study V58P4 were re-vaccinated one year later.

Studies Conducted to Support Annual Registration in Europe

The safety results of six studies conducted to support annual registration in Europe were submitted. Yearly studies of the immunogenicity and tolerability of seasonal influenza vaccines are required by the European Economic Community. The six registrational studies are listed below.

Table 56: Studies Conducted to Support Annual Registration

Study	Season	Total # Subjects	# Subjects ≥ 61 Years of Age*
V64P1S	2002-03	147	75
V71P1S	2003-04	112	54
V71P2S	2004-05	119	63
V71P3S	2005-06	110	58
V71P4S	2006-07	124	58
V71P5S	2007-08	125	62

*The number of elderly subjects represents a subset of the total number of subjects.

Source: BLA 125297, CSR, Table 2.7.6, page 1-2 and text of individual studies

All six studies were Phase 2, open-label, uncontrolled trials in healthy adult volunteers. All included a subset of subjects 60 years of age and older. Subjects were vaccinated with a single 0.5 mL dose of that season's influenza vaccine in the deltoid muscle on Day 0. Subjects were monitored in clinic for 30 minutes post-vaccination. Subjects were discharged from clinic with

diary cards, rulers, and thermometers to record solicited adverse reactions on the day of vaccination and during the subsequent three days post-vaccination. All had a three week safety follow-up for unsolicited AEs and serious AEs.

Information on local solicited adverse reactions is shown in the two tables below; the first table contains the results for subjects from 18 through 60 years of age, and the second includes the results for subjects 61 years of age and older.

Table 57: Percentage of Adults 18-60 Years of Age with Local Solicited Adverse Reactions in Yearly European Registrational Trials of Agriflu

	V64P1S	V71P1S	V71P2S	V71P3S	V71P4S	V71P5S
Pain	28%	21%	36%	25%	26%	21%
Induration	7%	7%	11%	2%	2%	3%
Swelling	4%	2%	7%	2%	2%	0
Erythema	3%	0	4%	0	0	0
Ecchymosis	1%	2%	0	2%	0	2%

Source: BLA 125297, CSR, Table 2 in each individual study report

Reviewer comment: Pain at the injection site was the most commonly reported local solicited AE in all of the studies, and was the only local solicited adverse reaction to be reported in more than 10% of subjects in all six studies. The next most common local solicited adverse reactions were induration and swelling. Erythema and ecchymosis were uncommon.

Table 58: Percentage of Adults 61 Years of Age and Older with Local Solicited Adverse Reactions in Yearly European Registrational Trials of Agriflu

	V64P1S	V71P1S	V71P2S	V71P3S	V71P4S	V71P5S
Pain	21%	4%	6%	0	10%	6%
Induration	3%	2%	2%	2%	2%	0
Swelling	7%	0	2%	0	2%	0
Erythema	5%	0	2%	0	0	0
Ecchymosis	1%	0	0	0	2%	0

Source: BLA 125297, CSR, Table 2 in each individual study report

Reviewer comment: As in other studies of Agriflu, local solicited adverse reactions were less common in elderly subjects than in younger adult subjects. Pain at the injection site was the most commonly reported local solicited reaction in elderly subjects; the percentage of subjects with pain ranged from 0% to 21%. The reason for this wide range is unclear. The study with the highest percentage of subjects with pain was V64P1S, which was the only study using a thimerosal-reduced formulation of Agriflu instead of a thimerosal-free formulation. However, it is unlikely that the thimerosal caused the higher percentage of elderly subjects with pain, because of the small amount of thimerosal and

because the increase in pain was not observed in the younger study population. All other local solicited adverse reactions were relatively uncommon in the elderly.

The percentage of subjects with individual systemic solicited adverse reactions is shown in the following two tables.

Table 59: Percentage of Adults 18-60 Years of Age with Systemic Solicited Adverse Reactions in Yearly European Registrational Trials of Agriflu

	V64P1S	V71P1S	V71P2S	V71P3S	V71P4S	V71P5S
Headache	15%	12%	13%	6%	14%	5%
Fatigue	7%	7%	16%	8%	8%	8%
Myalgia	8%	2%	13%	12%	8%	6%
Arthralgia	7%	3%	11%	8%	2%	11%
Sweating	4%	3%	9%	12%	5%	8%
Malaise	3%	3%	7%	4%	6%	3%
Chills	1%	0	4%	4%	3%	5%
Fever	0	0	0	0	2%	3%

Source: BLA 125297, CSR, Table 2 in each individual study report

Reviewer comment: Headache and fatigue were the most commonly reported systemic solicited adverse reactions in the younger adult study population. Headache was reported in 5% to 15% of subjects and fatigue in 7% to 16%. Myalgia, arthralgia, and sweating were each reported in more than 10% of subjects in at least one study. Fever and chills were fairly uncommon in these studies.

Table 60: Percentage of Adults 61 Years of Age and Older with Systemic Solicited Adverse Reactions in Yearly European Registrational Trials of Agriflu

	V64P1S	V71P1S	V71P2S	V71P3S	V71P4S	V71P5S
Headache	7%	4%	3%	3%	3%	5%
Fatigue	11%	2%	5%	2%	9%	8%
Myalgia	11%	2%	5%	7%	3%	6%
Arthralgia	7%	2%	2%	7%	2%	11%
Sweating	4%	0	2%	2%	3%	8%
Malaise	11%	4%	2%	5%	3%	3%
Chills	5%	0	2%	2%	0	5%
Fever	0	2%	0	0	0	3%

Source: BLA 125297, CSR, Table 2 in each individual study reports

Reviewer comment: In subjects 61 years of age and older, fatigue, myalgia, arthralgia, sweating, and malaise were all reported in more than 10% of subjects in one of the registrational studies. Each of the individual systemic solicited adverse reactions was

less common in the elderly than in younger adults; this may be due to immunosenescence. Fever and chills were also reported uncommonly in the elderly.

Unsolicited adverse events were not reported in all Clinical Study Reports. Vaccine-related unsolicited adverse events were reported for two subjects. One was an elderly subject with severe arthralgia and myalgia that started on Day 0 and lasted for 7 days. The other was an adult with the mild sensation of heat at injection site on Day 1, which lasted for one day.

Serious adverse events were reported in three subjects. In Study V71P2, a 68 year old female with a history of renal colic was hospitalized for renal colic and urosepsis two weeks post-vaccination. She was hospitalized for nine days, and was withdrawn from the study due to this AE. The SAE was not judged as related to Agriflu. In Study V71P3S, one subject had a tooth abscess and one had a joint dislocation; neither SAE was judged to be vaccine-related.

There were no study deaths.

Reviewer comment: Since unsolicited AEs were not included in the Clinical Study Reports for all of the studies, it is difficult to reach any conclusions regarding unsolicited AEs in these trials. In this reviewer's opinion, the serious AEs reported were not related to Agriflu. However, the usefulness of these results are limited by the short safety follow-up of three weeks.

Studies of Thimerosal-Free Formulations of Agriflu

Three Phase II trials, Studies V64P1, V71P1, and V71P2 were conducted to study the thimerosal-free formulation of Agriflu in comparison to a thimerosal-containing formulation of Agriflu. Elderly subjects only were enrolled in two of these studies, while both children and adults were enrolled in the third study.

Safety monitoring was identical in the three studies. Subjects received a single 0.5 mL dose of Agriflu in the deltoid and were observed for 30 minutes post-vaccination. Subjects were provided with diary cards, rulers, and thermometers. Solicited adverse reactions were followed for the day of vaccination and the subsequent three days. All three studies collected information on the same individual local and systemic solicited reactions. Unsolicited AEs were followed for 21 days.

Reviewer comment: Because this application is to support the thimerosal-free formulation of Agriflu, the safety results for that formulation only will be provided in this review. However, according to the applicant, there were no statistically significant differences between the two study arms in the percentage of study subjects with any of the individual solicited adverse reactions.

The study designs for V64P1 and V71P1 were similar; therefore, the safety results for these two studies will be presented together in this review. Studies V64P1 and V71P1 were Phase 2, observer-blind, randomized trials comparing thimerosal-free Agriflu formulations to thimerosal-containing formulations in elderly (61 years of age and older) subjects. In Study V64P1, 294 subjects were randomized in a 1:1 ratio to either thimerosal-free (TF) Agriflu or the formulation of Agriflu licensed in Europe at that time, which contained 0.05 mg of thimerosal per dose. In Study V71P1, 295 subjects were randomized in a 1:1 ratio to TF Agriflu or the Agriflu formulation marketed at that time, which contained trace amounts of thimerosal.

In both studies, the average age of study subjects was 69.5 years, the overwhelming majority of subjects were Caucasian, and the percentage of female and male subjects was similar.

The results for local and systemic solicited adverse reactions for the TF Agriflu arms of these studies are shown in the following table.

Table 61: Studies V64P1 and V71P1 - Percentage of Subjects with Solicited Adverse Reactions in the Thimerosal-Free Agriflu Vaccine Arms

	Study V64P1 N=147	**Study V71P1 N=147**
Local		
Pain	5%	5%
Swelling	2%	2%
Induration	1%	2%
Ecchymosis	1%	2%
Erythema	1%	1%
Systemic		
Myalgia	5%	5%
Headache	4%	5%
Fatigue	3%	5%
Malaise	3%	5%
Arthralgia	3%	2%
Sweating	2%	3%
Chills	2%	0
Fever	0	0

Source: BLA 125297, CSR, Study V6491, Table 9, page 52;
Study V71P1, Table 12.2.3-1, page 61

The most common local solicited adverse reaction in both studies was pain at the injection site, which was reported in 5% of subjects in each study. All other local solicited AEs were reported in a low percentage of subjects (1-2%). The most common systemic solicited adverse reactions

in the two studies were myalgia, headache, fatigue, and malaise, which all were reported in 3-5% of subjects. All solicited adverse reactions in these studies were reported at a low frequency.

> *Reviewer comment*: The percentage of subjects with solicited adverse reactions in these two studies was low. This is consistent with what has been observed in other studies of Agriflu in elderly subjects.

Unsolicited adverse events were reported in 4% of subjects in both studies. Thirteen unsolicited adverse events were reported in Study V64P1. These included AEs that were local and systemic adverse reactions that lasted past the four day collection period: pain, ecchymosis, arthralgia, myalgia, and malaise. The other unsolicited AEs in this study were nasopharyngitis, pharyngitis, cough, nausea, vomiting, cystitis, syncope, and dyspnea. In Study V71P1, the majority of unsolicited AEs were also solicited reactions lasting longer than the four day period; this included both local (ecchymosis, erythema, pain, induration/swelling, pruritis) and systemic (rigors, pyrexia) adverse events. Other unsolicited AEs reported were bronchitis, cough, nasopharyngitis, diarrhea, and nausea.

There were no serious AEs or deaths in either study.

Study V71P2 was also a Phase 2, observer-blind, controlled study comparing a new TF formulation of Agriflu to a formulation of TF Agriflu already licensed in Europe. Unlike the two studies just described, this study enrolled subjects from 3 to 60 years of age. Subjects were stratified into one of four age groups (3-5 years, 6-11 years, 12-17 years, and 18-60 years) and then randomized in a 1:1 ratio to one of the Agriflu arms.

The percentage of subjects with solicited adverse reactions is shown in the table below.

Table 62: Study V71P2 - Percentage of Subjects in Thimerosal-Free Agriflu Arm with Solicited Adverse Reactions by Age

	3-5 Years	**6-11 Years**	**12-17 Years**	**18-60 Years**
	N=57	**N=73**	**N=56**	**N=63**
Overall	35%	55%	48%	54%
Local	28%	49%	41%	40%
Systemic	12%	55%	48%	54%

Source: BLA 125297, CSR, Table 12.2.1-1, page 59

> *Reviewer comment*: The percentage of subjects with any solicited reaction, local solicited reactions, and systemic solicited adverse reactions were similar in the cohorts of subjects 6 years of age and older. The percentage of solicited adverse reactions was lowest in the youngest children. This may have been due to their inability to articulate AEs such as pain, headache, malaise, etc.

The results for individual local and systemic solicited adverse reactions for the TF Agriflu arms of these studies are shown in the following table.

Table 63: Study V71P2 - Percentage of Subjects with Individual Solicited Adverse Reactions by Age

	3-5 Years	6-11 Years	12-17 Years	18-60 Years
Local				
Pain	21%	38%	36%	38%
Swelling	4%	11%	9%	3%
Induration	9%	14%	11%	10%
Ecchymosis	0	5%	2%	3%
Erythema	7%	8%	2%	2%
Systemic				
Myalgia	5%	5%	11%	19%
Headache	4%	12%	14%	14%
Fatigue	5%	10%	9%	16%
Malaise	9%	8%	9%	14%
Arthralgia	4%	5%	5%	13%
Sweating	0	3%	7%	10%
Chills	5%	5%	0	10%
Fever	2%	0	0	0

Source: BLA 125297, CSR, Tables 12.2.3.1-4, pages 61-65

Pain was the most commonly reported local solicited adverse reaction. It was reported in more than one-third of subjects in all arms except children 3 to 5 years of age. Swelling and induration were reported in more than 10% of subjects in some study arms. Ecchymosis and erythema at the injection site were less commonly reported. The most frequently reported systemic adverse reactions were myalgia, headache, and fatigue. These were reported in up to 19% of subjects in any of the study arms.

> *Reviewer comment*: Most of the individual solicited adverse reactions were reported in fewer subjects in the 3-5 year age group as compared to older subjects. Some of these, such as malaise, arthralgia, and headache, may not have been reported because of the child's inability to articulate the symptom. Most solicited AEs that could have been reported by a care giver, such as induration and erythema, were reported in a similar percentage of subjects as in older study subjects.

Of the subjects who received the TF formulation, unsolicited adverse events were reported in five subjects in the 3-5 year age group, three in the 6-11 year age group, two in the 12-17 year age group, and five in the 18-60 year age group. The unsolicited AEs were erythema (3 subjects), ecchymosis (2 subjects), induration (2 subjects), cough (2 subjects) and one each of pyrexia, and pharyngitis.

Reviewer comment: Unsolicited AEs were fairly uncommon. This may be due in part to the short safety follow-up period.

There were no serious adverse events or deaths in this study.

Other Studies of Agriflu

Study V71P3 was a Phase 2, open-label, single-arm study at a single study center in Lithuania. This study site was located at a new site in which the applicant had not previously conducted studies.

The safety monitoring was identical to the other studies described above.

In this study 129 subjects were randomized and vaccinated with Agriflu; this included 64 subjects from 18-64 years of age and 65 subjects 61 years of age or older. All subjects were Caucasian; 65% of younger adult subjects were female and 58% of elderly subjects were female.

Solicited adverse reactions were reported by 37% of subjects in the 18-60 year age group and in 22% of subjects in the 61 years of age and older group. Individual solicited adverse reactions are shown in the table below.

Table 64: Study V71P2 - Percentage of Subjects with Solicited Adverse Reactions by Age Group

	18-60 years	≥61 Years
Local		
Pain	13%	8%
Swelling	2%	3%
Induration	5%	5%
Ecchymosis	3%	3%
Erythema	9%	3%
Systemic		
Headache	16%	6%
Myalgia	13%	2%
Fatigue	11%	5%
Malaise	6%	9%
Arthralgia	6%	8%
Sweating	6%	9%
Chills	2%	5%
Fever	0	0

Source: BLA 125297, CSR, Table 2, page 12

Reviewer comment: The percentage of subjects with individual solicited adverse reactions was lower for most AEs compared to other studies of Agriflu. The reason for this difference is unclear but might be related to inexperienced study personnel.

All of the solicited adverse reactions, except two, were of mild or moderate intensity. The two severe solicited AEs were severe sweating in an adult subject and severe fatigue in an elderly subject.

Most unsolicited adverse events were solicited adverse reactions lasting beyond study Day 3. These included 4 subjects with injection site erythema, 3 with arthralgia, 2 with sweating, and one each with injection site bruising, injection site erythema, injection site induration, injection site pruritis, malaise, and myalgia. Only one of these AEs was severe in intensity; severe arthralgia lasting for seven days was reported in an adult subject. Other unsolicited AEs were reported in five subjects; these AEs were animal bite, nasopharyngitis, radiculitis, pneumonia, and tibia fracture. None of these unsolicited AEs were judged as vaccine-related.

Reviewer comment: Most of the unsolicited AEs were due to solicited reactions lasting longer than the four day reporting period. Only one was severe. This reviewer agrees with the applicant's assertion that none of the other five unsolicited AEs were likely to be related to Agriflu.

There were no serious adverse events or deaths in this study.

Study V58P4E1

Study V58P4E1 was a re-vaccination study in which the subjects vaccinated in Study V58P4 were re-vaccinated one year after their vaccination in V58P4. The study design and results for Study V58P4 were previously described in this review and will not be repeated here.

In Study V58P4E1, subjects who had completed V58P4 (2609 subjects) were invited to enroll in the extension. Subjects were re-randomized so that subjects who received cell-derived vaccine in V58P4 could received either cell-derived vaccine or Agriflu in V58P4E1, and subjects who previously received Agriflu could receive either cell-derived vaccine or Agriflu in the study extension.

In Study V58P4E1, information on solicited adverse reactions was collected for 7 days post-vaccination, information on unsolicited AEs for 21 days post-vaccination, and information on SAEs for six months post-vaccination. The percentage of subjects with solicited adverse reactions is shown in the table below.

Table 65: Study V58P4E1 – Percentage of Subjects with Solicited Reactions

Solicited Adverse Reaction	**CD*/CD N=272**	**Agriflu/CD N=261**	**CD/Agriflu N=274**	**Agriflu/Agriflu N=260**
Any	33%	39%	31%	34%
Local	29%	32%	27%	29%
Systemic	15%	18%	17%	16%
Other#	6%	5%	4%	5%

*CD=cell-derived vaccine

#Other solicited reactions are 1) staying home due to solicited AE and 2) use of analgesic/antipyretic due to solicited AE

Source: BLA 125297, CSR, Table 2-3, page 23

> *Reviewer comment:* The percentage of subjects with solicited adverse reactions is similar in the four study arms.

The percentage of subjects with individual solicited adverse reactions was provided separately for adults and for the elderly. These results are shown in the following two tables.

Table 66: Study V58P4E1 – Percentage of Adult Subjects (18-60 Years of Age) with Individual Solicited Reactions

Adverse Reaction	CD*/CD N=272	Agriflu/CD N=261	CD/Agriflu N=274	Agriflu/Agriflu N=260
Local				
Pain	19%	24%	16%	18%
Erythema	12%	10%	9%	15%
Induration	6%	7%	4%	8%
Ecchymosis	5%	5%	4%	5%
Swelling	3%	3%	1%	5%
Systemic				
Headache	9%	10%	8%	8%
Myalgia	7%	7%	7%	8%
Fatigue	7%	9%	7%	9%
Malaise	7%	10%	7%	8%
Arthralgia	4%	4%	3%	3%
Sweating	4%	5%	3%	4%
Chills	3%	3%	1%	2%
Fever	1%	0	1%	1%
Other				
Stayed home	1%	1%	1%	2%
Analgesic/antipyretic use	5%	4%	4%	4%

*CD=cell-derived vaccine

Source: BLA 125297, CSR, Table 2-4, page 24

Pain was the most commonly reported local solicited AE, and headache was the most commonly reported systemic solicited AE.

> *Reviewer comment*: The percentage of adults with each individual solicited adverse reaction is similar in the four study arms; in addition, the percentages observed in the study extension are similar to those observed in the original study.

Table 67: Study V58P4E1 – Percentage of Elderly Subjects (≥ 61 Years of Age) with Individual Solicited Reactions

Adverse Reaction	CD*/CD N=290	Agriflu/CD N=281	CD/Agriflu N=297	Agriflu/Agriflu N=300
Local				
Pain	8%	9%	7%	6%
Swelling	2%	3%	2%	1%
Induration	3%	5%	2%	3%
Ecchymosis	4%	4%	5%	6%
Erythema	8%	9%	6%	5%
Systemic				
Headache	6%	6%	7%	5%
Myalgia	4%	7%	3%	3%
Fatigue	8%	9%	8%	5%
Malaise	7%	10%	6%	7%
Arthralgia	5%	5%	5%	4%
Sweating	3%	6%	3%	2%
Chills	3%	4%	2%	2%
Fever	1%	0	0	<1%
Other				
Stayed home	1%	2%	1%	1%
Analgesic/antipyretic use	2%	4%	3%	3%

*CD=cell-derived vaccine

Source: BLA 125297, CSR, Table 2-7, page 27

Reviewer comment: The percentages of individual solicited adverse reactions were similar in the four study arms. As in other studies of Agriflu, the frequency of individual adverse reactions was lower in elderly subjects than in younger adult subjects. The results in Study V58P4E1 were similar to those in V58P4.

The percentage of subjects with unsolicited AEs during the three weeks after vaccination is shown in the table below.

Table 68: Study V58P4E1 – Percentage of Subjects with Unsolicited Adverse Events by Age

	CD*/CD N=272	Agriflu/CD N=261	CD/Agriflu N=274	Agriflu/Agriflu N=260
18-60 Years	10%	9%	7%	8%
≥ 61 Years	7%	9%	5%	6%

Source: BLA 125297, CSR, Tables 12.2.1.1-2 and 12.2.1.1-2, pages 103 and 106

The system organ class with the highest percentage of unsolicited AEs was infections and infestations. The most common AE in that class was rhinitis. The other two most frequently involved system organ classes (> 2% of subjects) were general disorders and administrative site conditions in both age groups, respiratory, thoracic, and mediastinal disorders in younger adults, and musculoskeletal, connective tissue, and bone disorders in elderly subjects. There were no severe unsolicited AEs in adult subjects, and the majority of AEs in the elderly were also mild or moderate in severity. There were six severe AEs in the elderly population (acute myocardial infarction in three subjects, hypertension in one subject, forearm fracture in one subject, and nasal congestion in one subject).

> *Reviewer comment*: The percentage of subjects with unsolicited AEs was similar in the four study arms and in both age groups.

Serious AEs in the first three weeks post-vaccination were reported in one adult subject and in six elderly subjects. The adult subject was hospitalized for chest pain on Day 14. SAEs reported in elderly subjects were myocardial infarction in three subjects and atrial fibrillation, chest pain, and forearm fracture in three subjects each. None of the SAEs was judged as related to the study vaccine. There were no deaths within three weeks of vaccination.

Fifteen SAEs were reported in 13 adult subjects during the three week to six month follow-up period. The types of SAEs were provided as system organ classes. Of the 15 SAEs, three were gastrointestinal disorders, three were neoplasms, and one each were cardiac, hepato-biliary, infectious, musculoskeletal, nervous system, psychiatric, procedure, and general. There was one death in an adult subject in this time period. The exact date of death was unknown; the cause of death was suicide by drug overdose.

There were 62 serious AEs in elderly subjects during the period from three weeks to six months post-vaccination. This includes four deaths. The organ system classes involved are listed below.

Table 69: Study V58P4E1 – Number of Subjects with Serious Adverse Events by System Organ Class

System Organ Class	# Subjects
Cardiac	8
Ear and Labyrinth	1
Eye	1
Gastrointestinal	5
General and Administration Site	2
Hepato-biliary	4
Infections and Infestations	5
Injury and Poisoning	5
Investigations	1
Musculoskeletal, Connective Tissue and Bone	3
Neoplasm	5
Nervous System	2
Renal and Urinary	2
Reproductive System and Breast	2
Respiratory, Thoracic, and Mediastinal	3
Skin and Subcutaneous Tissue	1
Surgical and Medical Procedures	3
Vascular	3

Source: BLA 125297, CSR, Table 12.3.1.2-2, page 16

The four deaths in elderly subjects were due to myocardial infarction, sudden cardiac death, acute pancreatitis, and cerebral hemorrhage. None were judged as vaccine related.

> *Reviewer comment*: The serious adverse events and deaths in Study V58P4E1 were consistent with illnesses commonly reported in the study population. There was no increase in the frequency of SAEs or deaths in a single organ system or of a single individual AE.

There were three pregnancies in this study. Two of the subjects delivered full term, healthy babies, and the other subject was lost to follow-up.

9 Overview of Efficacy (Immunogenicity) Across Trials

The immunogenicity of Agriflu is primarily demonstrated by results from the two pivotal studies, Study V71P5 and V71P6 with additional support from Studies V58P4 and V58P9. Both pivotal studies were randomized, observer-blind, controlled studies. The active comparator for both

studies was Fluvirin, an influenza vaccine licensed for use in the United States and also manufactured by Novartis Vaccines and Diagnostics.

In the two pivotal studies, the immunogenicity of Agriflu was measured by endpoints and criteria described in the FDA Guidance for Industry, "Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines." The two endpoints were: 1) proportion of subjects with seroconversion at Day 21 (four fold rise in HAI titers or change from undetectable to a titer of ≥ 1:40) and 2) proportion of subjects achieving a HAI titer ≥ 1:40 at Day 21. Responses for these endpoints were measured against pre-defined criteria for these two endpoints as described in the Guidance. The immunogenicity results for the two primary studies are shown in the following table.

Table 70: Hemagglutination-Inhibiting (HI) Antibody Responses to Agriflu in the Two Pivotal Clinical Trials (Adults 18 Years of Age and Older)

	V71P5 (N=424)			**V71P6 (N=1182)**		
	A/H1N1	**A/H3N2**	**B**	**A/H1N1**	**A/H3N2**	**B**
Seroconversion Rate	74%	72%	77%	94%	67%	84%
LL 95%CI*	69%	68%	72%	93%	65%	82%
% of Subjects with HI≥1:40 Post-Vaccination	93%	96%	91%	98%	99%	87%
LL 95%CI*	90%	94%	87%	97%	98%	85%

*LL 95% CI is the lower limit of the 95% confidence interval.
Source: BLA 125297, CSRs, Table 11.4.1.1-1, page 66 and Table 11.4.1.2.1-1, page 50

As shown in the table above, the results for the proportion of subjects with seroconversion and the percentage of subjects with HI titers of 1:40 or greater after vaccination with Agriflu met the target criteria for both influenza A strains and for the influenza B strain.

The results of two other immunogenicity studies, V58P4 and V58P9, were included as additional support of efficacy. Both of these trials were randomized, observer-blind studies in which Agriflu was the active control for an experimental cell-derived seasonal influenza vaccine. The immunogenicity results for Agriflu are shown in the table below.

Table 71: Point Estimates (Lower Bound 95% Confidence Interval) for HI Titers in Supportive Immunogenicity Studies of Agriflu

	18-60 Years of Age		**≥61 Years of Age**
	V58P4 N=644	**V58P9 N=168**	**V58P4 N=674**
Seroconversion Rate			
H1N1	67% (63%)	77% (70%)	55% (51%)
H3N2	64% (60%)	88% (82%)	65% (61%)
B	81% (78%)	70% (63%)	73% (70%)
Post-Vaccination % of Subjects with HI Titers≥1:40			
H1N1	92% (89%)	95% (91%)	85% (82%)
H3N2	99% (98%)	96% (92%)	98% (97%)
B	91% (88%)	88% (82%)	89% (87%)

Source: BLA 125297, CSR, Tables 11.4.1.1-1 – 14.1.1.-3 and 11.4.1.2-1 – 1.4.1.2-3 pages 80-85, and Tables 11.4.1-2 – 14.1-4 pages 72-76

As in the pivotal trials, in the supportive studies, the results for the percentage of subjects with seroconversion and the percentage of subjects with HI titers of 1:40 or greater after vaccination with Agriflu met the target criteria for both influenza A strains and for the influenza B strain.

The results of a third study, V58P2 were submitted at the request of CBER. This study was similar in design to Study V58P4, but the sample size was smaller and the study was conducted in a study population in which a large percentage of subjects had previously been vaccinated against influenza. The seroconversion rate for all three strains and in both age groups did not meet the criteria described in the FDA Guidance for Industry. Only the percentage of subjects with post-vaccination titers of 1:40 or higher for the A/H3N2 met the CBER criteria. The reason for the poor outcome in this study is unclear but may be related to the high percentage of subjects who had been previously vaccinated. It also must be noted that this study was designed to satisfy criteria used by the EMEA and was not designed to support licensure in the United States.

In the opinion of this reviewer, the results from the two pivotal studies and the two supportive studies support the immunogenicity and consistency of manufacture of Agriflu.

10 Overview of Safety Across Trials

The primary support for the safety of Agriflu was the results of the two pivotal studies, V71P5 and V71P6, which were randomized, observer-blind studies comparing Agriflu to Fluvirin in healthy adult volunteers. A total of 692 adults from 18 to 64 years of age were randomized and vaccinated in Study V71P5; 1493 adults 18 to 49 years of age were randomized and vaccinated in study V71P6. Additional support for Agriflu safety was also provided by the safety results of 1) six European annual re-registration studies, 2) three studies comparing thimerosal-free and

thimerosal-reduced formulations, 3) the re-vaccination study of subjects in V58P4, and 4) a pilot study conducted at a new study site.

The safety assessments in the studies were similar. Solicited adverse reactions were collected for the day of vaccination and for the six subsequent days in the two pivotal trials and for the day of vaccination and the three subsequent days in the supportive trials. Unsolicited adverse events were followed for the 21 days post-vaccination. Information on serious adverse events was collected for the entire study period.

The adverse events observed most commonly in the seven days after vaccination with Agriflu were local events. Across all studies of Agriflu, pain at the injection site was the most commonly reported solicited adverse reaction and was reported in 22% and 25% in the two pivotal trials. The other solicited adverse events were reported less commonly: induration was reported in 5%-10%, swelling in 4%-6%, erythema in 5%-6%, and ecchymosis in 5%-6% of subjects in the two pivotal trials. The systemic solicited adverse reactions reported in more than 5% of subjects in either pivotal trial were headache (23%-24% of subjects), myalgia (14%-18% of subjects), malaise (12% of subjects in both studies), fatigue (9%-10% of subjects), arthralgia (5%-6% of subjects), and chills (5%-7% of subjects). The safety results of the supportive studies were similar to those of the two pivotal trials.

Information on spontaneous adverse events was reported in all studies of Agriflu. The most commonly reported spontaneous AEs included nasopharyngitis, rhinitis, and pharyngeal pain, and headache. No events of Guillain-Barré, anaphylaxis, or oculo-respiratory syndrome were reported in these studies.

10.1 Deaths

In the clinical studies included in this BLA, there were a total of four deaths in subjects who received Agriflu. All were reported in subjects 61 years of age and older; deaths were due to hypertension,, cerebral hemorrhage, acute pancreatitis, and lung adenocarcinoma.. None of these deaths was judged as related to Agriflu. All of the causes of death were consistent with illnesses typically seen in elderly individuals.

10.2 Human Reproduction and Pregnancy Data

There were 10 pregnancies in the clinical studies included in this BLA. Four pregnancies ended in spontaneous abortions. One of these was associated with a motor vehicle accident. Conception was estimated at approximately the time of vaccination for the other three spontaneous abortions; therefore, all were included as serious adverse events. There was a single induced abortion. Four pregnancies ended in the birth of healthy, term infants. One pregnant subject was lost to follow-up. The number of pregnancies was small; no conclusions can be reached by these data.

10.3 Safety Conclusions

The adverse events most commonly observed after vaccination with Agriflu were local events at the injection site, particularly pain. The most common systemic event was headache. No evidence for an increase in severity or seriousness of adverse events in subjects who received Agriflu was observed by this reviewer. Therefore the safety profile of Agriflu was acceptable for clinical approval of this application.

11 Additional Clinical Issues

11.1 Dose Regimens and Administration

Agriflu is available as 0.5 mL single-dose prefilled syringes. Agriflu should be administered as a single 0.5 mL injection by the intramuscular route preferably into the region of the deltoid muscle of the upper arm.

11.2 Special Populations

Gender:

On analysis of the immunogenicity results from the two pivotal studies, there was no difference in serum HAI response by gender.

Race/Ethnicity:

The overwhelming majority of subjects in the three studies included in this supplement were White / Caucasian. However, there is no known difference in antibody or clinical response to seasonal influenza vaccines by race or ethnicity.

Geriatrics:

Subjects 65 years of age and older were enrolled in 12 of the clinical studies included in this BLA. A total of 1117 elderly subjects were vaccinated with Agriflu in these studies. Subjects 65 years of age and older were not included in the two pivotal trials, but were enrolled in the two supportive immunogenicity studies, V58P2 and V58P4. Subjects in these studies were stratified by age (18-60 and ≥ 61 years) and then randomized to either Agriflu or a cell-derived vaccine. The applicant performed a post hoc analysis of subjects 65 years of age and older. Eighty-six subjects 65 years of age and older were enrolled in Study V58P2, and 985 were vaccinated in Study V58P4. The percentage of elderly subjects with post-vaccination HI titers of 1:40 or greater and the percentage who seroconverted in these two studies are shown in the table below.

Table 72: Point Estimates and Lower Bound of 95% Confidence Interval for Percentage of Elderly Subjects (≥ 65 Years) with Post-Vaccination HI Titers ≥ 1:40 and with Seroconversion in Studies V58P2 and V58P4

	Study V58P2		**Study V58P4**	
	Agriflu N=48	**Cell-Derived Vaccine N=38**	**Agriflu N=481**	**Cell-Derived Vaccine N=504**
Percentage of Subjects with Post-Vaccination HI Titers ≥ 1:40				
A/H1N1	71% (56%)	79% (63%)	85% (82%)	86% (83%)
A/H3N2	92% (80%)	95% (82%)	98% (96%)	97% (95%)
B	38% (24%)	39% (24%)	90% (87%)	90% (87%)
Seroconversion Rate				
A/H1N1	10 (3%)	8% (2%)	55% (51%)	55% (50%)
A/H3N2	10% (3%)	32% (18%)	64% (60%)	68% (64%)
B	31% (19%)	34% (20%)	74% (69%)	80% (76%)

Source: BLA 125297, Clinical Overview, Table 2.5.4.4-2, page 17

As noted earlier in this review, the percentage of subjects with post-vaccination titers of 1:40 or greater and the seroconversion rate were lower in Study V58P2 than in Study V58P4. The reason for this difference is not entirely clear but may have been related to the high rates of previous influenza vaccination in study V58P2. In Study V58P4, the CBER criteria to successfully demonstrate immunogenicity were met for all three strains and for both the seroconversion rate and the percentage of subjects with post-vaccination HI titers of 1:40 or greater. Solicited adverse events were reported in a lower percentage of elderly subjects than in younger adult subjects. In general, there were more unsolicited adverse events and serious adverse events in elderly subjects, but these were usually not judged as vaccine related and were consistent with illnesses commonly observed in the elderly.

These data demonstrated acceptable safety and immune response when Agriflu was administered in an elderly population, but an additional immunogenicity and safety study comparing Agriflu to a U.S.-licensed comparator in the elderly will be requested as post-marketing commitment.

11.3 Pediatrics

Although the indication for Agriflu will not include children, the BLA submission contains limited immunogenicity and safety data from children from 3 to 17 years of age. A total of 802 children were randomized and vaccinated with Agriflu in Study V71P5. Due to irregularities in the HI titer results, data from one-fourth of the children from 3 to 8 years of age were excluded from the immunogenicity analysis.

The Applicant has agreed to conduct two studies of Agriflu in pediatric patients. These studies will include children from 6 months to 17 years of age.

12 Conclusions – Overall

The clinical data submitted in this BLA support the safety and immunogenicity of Agriflu when administered to adults 18 years of age and older. The clinical recommendation for accelerated approval of Agriflu is based on its effect on a surrogate endpoint that is reasonably likely to predict that patients will derive clinical benefits from Agriflu. Two pivotal randomized, active controlled studies showed that subjects who received Agriflu had immune responses that successfully met all of the pre-defined criteria for antibody response to influenza vaccination. The safety concerns are primarily mild to moderate local injection site reactions; mild to moderate systemic adverse events are reported less commonly and are typically self-limited.

13 Recommendations

13.1 Approval, Non-approval, Conditions

In the opinion of this reviewer, the immunogenicity and safety data submitted in this application support the approval of this BLA under the accelerated approval regulations.

13.2 Recommendation on Postmarketing Actions

The Applicant has agreed to the following postmarketing commitments.

1. Novartis Vaccines and Diagnostics agrees to submit the results of Study No. V58P13, a placebo-controlled clinical endpoint efficacy and safety study of Novartis's *Agriflu*® in healthy adults 18 to 49 years of age. The final study report for the study will be submitted by June 30, 2009.

2. Novartis Vaccines and Diagnostics agrees to conduct Study No. V71_18, a randomized, observer-blind, non-inferiority immunogenicity and safety study with Novartis's *Agriflu*® and a US Licensed Trivalent Inactivated Split-Virion Influenza Vaccine in a pediatric population from 3 years to 17 years. The final protocol for this study will be submitted by December 31, 2009. The study will be conducted in 2010. The final study report will be submitted by June 30, 2013.

3. Novartis Vaccines and Diagnostics agrees to conduct Study No. V71_20, a randomized, observer-blind, immunogenicity and safety study with Novartis's *Agriflu*® and a US Licensed Trivalent Inactivated Split-Virion Influenza Vaccine in a pediatric population from 6 months to less than 3 years of age. The final protocol for this study will be submitted by December 31, 2010. The study will be conducted in 2011. The final study report will be submitted by June 30, 2013.

4. Novartis Vaccines and Diagnostics agrees to establish a pregnancy registry to prospectively collect data on spontaneously-reported exposures to Agriflu during pregnancy. A protocol for this pregnancy registry will be submitted by June 30, 2010.

This protocol will address elements found in FDA's guidance for Industry on Establishing Pregnancy Exposure Registries (9/2/2002).

5. Novartis Vaccines and Diagnostics agrees to conduct a non-inferiority immunogenicity study with Agriflu and a US-licensed trivalent inactivated seasonal influenza vaccine in a population of adults 50 years of age and older. The final study protocol for this study will be submitted by June, 2010. This study will start by March 2013. The final study report will be submitted by November 2014.

13.3 Labeling

Revisions to the package circular were negotiated with the Applicant. The main issues discussed were:

- the amount of immunogenicity and safety data for pediatric subjects and for subjects 65 years of age and older included in the package insert, and
- inclusion of language about the lack of clinical endpoint data.