

Application Type	Original Application
STN	125408/0
CBER Received Date	November 22, 2011
PDUFA Goal Date	September 21, 2012
Division / Office	DVRPA /OVR
Priority Review	No
Reviewer Name(s)	Lucia Lee, M.D. for Melisse Baylor, M.D. Medical Officer, Clinical Trials Review Branch 1 (CRB1)
Review Completion Date / Stamped Date	November 20, 2011
Supervisory Concurrence	Jeff Roberts, M.D. Chief, CRB1
Applicant	Novartis Vaccines and Diagnostics, Inc.
Established Name	Influenza Vaccine (MDCK Cells)
(Proposed) Trade Name	Flucelvax
Pharmacologic Class	Vaccine
Indication(s) and Intended Population(s)	Active immunization for the prevention of disease caused by influenza virus subtypes A and type B contained in the vaccine. Flucelvax will be approved for use in persons 18 years of age and older.
Dosage Form and Route of Administration	Suspension for injection supplied in single dose 0.5 mL pre-filled syringe to be administered by intramuscular injection
Dosing Regimen	Single dose
Formulation	The 2012-2013 vaccine contains hemagglutinins from two influenza A subtypes (A/H1N1, A/H3N2), and one influenza B type

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GLOSSARY

ACIP = Advisory Committee on Immunization Practices
AE = adverse event
BLA = Biologic License Application
CDC = Centers for Disease Control
CFR = Code of Federal Regulations
CHMP = Committee for Medicinal Products for Human Use (EMA)
CI = confidence interval
CMC = chemistry, manufacturing, and controls
CSR = clinical study report
EMA = European Medicines Agency
GMR = geometric mean ratio
GMT = geometric mean titers
HAI = hemagglutination inhibition assay
HA= hemagglutinin
ICH = International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ILI = influenza-like illness
IND = Investigational new drug
ISE = integrated summary of efficacy
ISS = integrated summary of safety
ITT = intent-to-treat
LB = lower bound
MedDRA = Medical Dictionary for Regulatory Activities
MI = myocardial infarction
MITT = modified intent-to-treat
mL = milliliter
N = number
NCT = National Clinical Trials
N/E = not evaluable
PeRC = Pediatric Review Committee
PCR = polymerase chain reaction
PI = package insert
PMC = postmarketing commitment
PMR = postmarketing requirement
PREA= Pediatric Research Equity Act
PP = per protocol
SAE = serious adverse event
SCR = seroconversion rate
SMCA = Lithuania Competent Authority (regulatory authority for Lithuania)
TIV = trivalent inactivated, influenza vaccine

1. EXECUTIVE SUMMARY

Flucelvax is a trivalent, inactivated subunit influenza vaccine manufactured from virus propagated in Madin Darby Canine Kidney (MDCK) cells, a continuous cell line.

1.1 Recommendation for Regulatory Action

In the judgment of this clinical reviewer, the data submitted in the license application support the traditional approval of Flucelvax for active immunization for the prevention of disease caused by influenza virus A subtypes H1N1 and H3N2 and type B contained in the vaccine, in persons 18 years of age and older. The recommendation for the traditional approval of Flucelvax is primarily based on the efficacy of Flucelvax in the prevention of culture-confirmed influenza illness caused by community-acquired influenza strains similar to those contained in the vaccine. Vaccine efficacy was demonstrated in a randomized, placebo-controlled, clinical efficacy study in 11,299 adults 18 through 49 years of age. In this study, the influenza attack rate for Flucelvax recipients was 0.19%, compared to 1.14% in placebo recipients for an overall vaccine efficacy of 83.8% (LB of one sided 97.5% CI: 61.0%). The effectiveness of Flucelvax in adults older than 49 years of age (age range: 50 through 70 years), was demonstrated in a randomized study of 2,654 subjects in which the antibody response (HAI) to Flucelvax was non-inferior to the antibody response to a vaccine licensed in the US for use in this age range. The safety data from four additional studies included in this application provide added support for the conclusion that Flucelvax is safe for use in adults 18 years of age and older. The most commonly reported adverse events associated with Flucelvax were local reactions at the injection site (pain and erythema), headache, fatigue, myalgia, and malaise. No individual adverse events or pattern of adverse events were associated with the administration of Flucelvax. Therefore, the potential benefits of administration of Flucelvax outweigh the potential risks. In addition, the approval of Flucelvax may provide meaningful benefit as the first influenza vaccine manufactured in cell culture instead of eggs, which may allow for a more rapid production of influenza vaccines and quicker manufacturing response to newly circulating influenza strains.

1.2 Recommendation on Postmarketing Actions

The applicant has agreed to submit the results of Study V58P12, a Phase 2/3, randomized, observer-blind, active-controlled, study to support the safety and effectiveness of Flucelvax in children from 4 through 17 years of age. This study was conducted in the 2007-2008 influenza season. For additional support of the safety and immunogenicity of Flucelvax in children, the applicant has also agreed to conduct a randomized, observer-blind, active-controlled, safety study (V58_31) in children 4 through 17 years of age, a dose finding study (V58P16) in children 6 months to < 4 years of age, and a safety and immunogenicity study (V58_35) to compare Flucelvax to a US-licensed influenza vaccine in children 6 months to < 4 years of age. These studies will be required under PREA. The applicant has also agreed to conduct a clinical lot consistency study using vaccine produced at its US manufacturing site; this study will be conducted in healthy adults and will evaluate the immunogenicity of three consecutively manufactured lots. Finally, the Applicant has agreed to establish a pregnancy registry to collect data prospectively on spontaneously-reported exposures to Flucelvax during pregnancy.

1.3 Summary of Clinical Findings

The conclusions about the safety and effectiveness of Flucelvax were primarily based on the safety and clinical endpoint results from Study V58P13, a randomized, blinded, placebo-controlled clinical efficacy study conducted in the United States and Finland in 11,299 healthy adult volunteers 18 through 49 years of age. Subjects were randomized in a 1:1:1 ratio to receive Flucelvax, Agriflu, or phosphate buffered saline placebo. Active and passive surveillance for influenza-like illnesses (ILI) was conducted throughout the 2007-2008 influenza season. An ILI was defined as any two of the following signs/symptoms: fever/feverish, body aches, cough, sore throat, chills, headache, and runny/snuffy nose. Nasal and throat swabs were collected from subjects with ILIs within 72 hours of onset; these swabs were sent for influenza virus culture. The primary efficacy endpoint was illness caused by virus culture-confirmed community-acquired influenza wild-type strains antigenically similar to those contained in the vaccines. The incidence of virus culture-confirmed influenza in the two active arms (Flucelvax and Agriflu) was compared independently to that in the placebo arm. The efficacy of Flucelvax was considered to be demonstrated if the lower limit of the one-sided 97.5% confidence interval for the vaccine efficacy was above 40%.

The percentage of subjects who were culture positive for influenza strains matching those contained in the vaccine was 0.19% in Flucelvax recipients and 1.14% in placebo recipients. Results for the primary endpoint are shown in the following table.

Table 1: Attack Rates and Vaccine Efficacy against Vaccine Matched, Culture-Confirmed Influenza in Study V58P13

	Total # subjects	# Subjects with Influenza	Attack Rate	Vaccine Efficacy (vs. Placebo)	97.5% CI*
Flucelvax	3776	7	0.19%	83.8%	61.0%
Placebo	3843	44	1.14%	--	--

*97.5% CI=lower bound of one-sided 97.5% confidence interval

Source: BLA 125297/1, CSR for V58P13, Table 11.4.1.1.1-1, page 73

As shown above, the vaccine efficacy for Flucelvax was 83.8% with a lower bound, one-sided 97.5% confidence interval of 61.0%. The results met the criteria outlined in the study protocol to demonstrate vaccine efficacy.

The use of Flucelvax in individuals 50 years of age and older is primarily supported by results from Study V58P4. In this study, Flucelvax was demonstrated to be immunologically non-inferior to Agriflu, which is licensed in the United States for use in subjects 18 years of age and older, including in the age subgroups, 18 through 49 years, and 65 years of age and older. Results in both age groups are shown in the following tables.

Table 2: Study V58P4 - Percentage (%) of subjects with Post-Vaccination HI Titers \geq 1:40 and Seroconversion Rate in Flucelvax Recipients 65 Years of Age and Older

<u>Vaccine strain</u>	<u>% of Subjects with HI Titer \geq1:40 (95% CI %)</u>	<u>% of Subjects with Seroconversion (95% CI %)</u>
<u>A/H1N1</u>	<u>86</u> (83-89)	<u>55</u> (50-59)
<u>A/H3N2</u>	<u>97</u> (95-98)	<u>68</u> (64-72)
<u>B</u>	<u>90</u> (87-93)	<u>80</u> (76-84)

Source: BLA 125408/0, Section 1.14.1.2

Table 3: Study V58P4 - Non-inferiority Analysis of FLUCELVAX to a US licensed Comparator (Agriflu) in Adults 65 Years of Age and Older

	Vaccine Group Ratio/Difference (95% CI) Flucelvax Versus Agriflu		
	A/H1N1	A/H3N2	B
GMTs ratio (Flucelvax / Agriflu)	1.06 (0.92, 1.22)	0.97 (0.84, 1.12)	1.28 (1.1, 1.48)
Difference in Seroconversion Rates (Flucevax – Agriflu)	-1% (-7, 6)	3% (-2, 9)	7% (1, 12)

Source: BLA 125408/0, Section 1.14.1.2

As shown in Tables 2 and 3, non-inferiority of Flucelvax to Agriflu was demonstrated in both age groups for all three strains by analyses of geometric mean titer ratios and by the difference in seroconversion rates.

The results of seven clinical trials were included in this BLA submission. In these studies, a total of 5,682 subjects received a single, 0.5 mL dose of Flucelvax. The most frequently reported adverse events were solicited adverse reactions reported in the week post-vaccination. The types of solicited adverse reactions queried were identical in each study. Adverse reactions reported in 10% or more of adult subjects from 18 through 64 years of age were pain at the injection site, erythema at the injection site, myalgia, and malaise. Adverse reactions reported in 10% or more of subjects 65 years of age and older were erythema at the injection site, fatigue, headache, and malaise. The majority of these adverse reactions were mild; severe individual solicited adverse reactions were reported in 1% or fewer of subjects.

There were seven deaths in subjects who received Flucelvax, five in subjects who received Agriflu and one in a subject who received placebo. Two deaths occurred within one month of vaccination: a 57 year old subject died due to intentional drug ingestion (suicide) on an unknown date that was within one month of vaccination with Flucelvax and a 73 year old died on Day 25

due to carbon monoxide poisoning from a house fire. None of the deaths was judged as vaccine-related by the investigators or by this reviewer.

Serious adverse events were reported in 1% of subjects from 18 to 64 years of age who received Flucelvax and in 1% of subjects from 18 to 64 years of age who received an active control. SAEs were reported in 4% of elderly subjects who received Flucelvax and in 4% of elderly subjects who received active control. Serious adverse events were reported within one week of vaccination in five subjects: acute myocardial infarction, atrial fibrillation, and joint contracture in the Flucelvax arm, appendicitis in the active control arm, and two subjects with pharyngitis in the placebo arm. None of these SAEs was judged as vaccine-related by the investigator or by this reviewer.

No cases of Guillian-Barré syndrome or anaphylaxis were reported in subjects who received Flucelvax. There was one report of hypersensitivity, in which the subject developed hoarseness on the day of vaccination and was treated with antihistamines but not hospitalized. This adverse event was judged as related to study vaccine. Another subject was diagnosed with erythema multiforme seven days post-vaccination. This subject also responded to antihistamines. No increase in the number of subjects with urticaria or other adverse events that might be associated with an allergic reaction was observed in subjects who received Flucelvax.

No evidence for an increase in severity or seriousness of adverse events was observed by this reviewer. Therefore, the safety profile of Flucelvax was acceptable for approval of this application, given the overall benefit-risk balance.

1.4 Compliance with Pediatric Research Equity Act (PREA)

The pediatric development plan for Flucelvax was presented to and approved by the Pediatric Review Committee on August 22, 2012. The study of Flucelvax in children from birth to < 6 months of age was waived because Flucelvax does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of infants < 6 months of age. Available data indicate that serum antibody responses to inactivated influenza vaccines in infants < 6 months of age are not as robust as in older children due to inherent immaturity of the immune system and interference from maternal antibody.

Since Flucelvax was ready for approval in adults, the submission of pediatric studies in children from 6 months to 17 years of age was deferred. The applicant has agreed to submit the results of two studies to support the safety and immunogenicity of Flucelvax in children 4 years of age to 17 years of age and the results of two additional studies to support the safety and immunogenicity of Flucelvax in children from 6 months to < 4 years of age.

2. CLINICAL AND REGULATORY BACKGROUND

Flucelvax is an inactivated, cell culture-derived influenza virus vaccine. It is indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.

2.1 Disease or Health-Related Condition(s) Studied

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 older

than 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) recommends routine influenza vaccination annually for all persons six months of age and older. The ACIP recommendations also support additional efforts or programs to focus on vaccination of persons at higher risk for influenza-related complications, which includes but is 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.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

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

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™, Fluvirin™, Fluarix™, Afluria™, FluLaval™, and Agriflu™. All of these vaccines are produced in embryonated hen eggs. Fluarix, Afluria, FluLaval, and Agriflu were approved using the accelerated approval mechanism because of the shortage of influenza vaccine. Accelerated approval of these vaccines was based on immunogenicity and safety data from studies using a surrogate marker (anti-hemagglutinin antibody response) to predict clinical efficacy. The clinical efficacy of Fluarix, Afluria and Agriflu was confirmed in clinical endpoint studies, and all three vaccines now have traditional approval. The clinical endpoint study used to support traditional approval of Agriflu is the same study being used to support the traditional approval of Flucelvax.

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. Clinical efficacy results are also included in the FluMist package insert.

All of these approved influenza vaccines are manufactured in eggs (i.e., are egg-derived or egg based). Flucelvax would be the first cell-derived influenza vaccine licensed in the United States. Egg based vaccines are dependent on the egg supply and as a result, there have been vaccine delays when eggs have been in short supply. It is also difficult to scale up production because of the need for additional eggs. In addition, influenza vaccine production times are dependent on the time it takes for the vaccine antigens to grow in eggs. Finally, the final vaccine products contain egg protein; and therefore, there is no licensed influenza vaccine available for use in persons with egg allergy. Flucelvax is manufactured in MDCK (Madin Darby canine kidney) cells. This manufacturing process removes the dependence on eggs and the egg supply in the production process. Therefore, it may be easier to scale up production and production timelines might be shorter. Although this might allow for production of influenza vaccines when circulating strains differ than those predicted, the need for strain specific potency reagents may limit the ability to shorten the production timelines. The amount of egg protein in Flucelvax is expected to be at least ----(b)(4)----- fold lower than the amount that is generally detectable in

influenza vaccine produced in eggs, so its licensure might provide an acceptable influenza vaccine for persons with egg allergy. However, it is difficult to quantify the exact amount of egg proteins and Flucelvax, and it must be noted that Flucelvax has not been studied in individuals with egg allergies.

2.3 Safety and Efficacy of Pharmacologically Related Products

Flucelvax will be the first cell-derived, trivalent, inactivated influenza vaccine to be approved in the United States. The other approved influenza vaccines are manufactured in eggs. Even though the production of Flucelvax included using a cell line rather than eggs the manufacturing process has enough similarities so that the safety and efficacy of egg-based vaccines are likely to be similar to the safety and efficacy of Flucelvax.

The efficacy of Flucelvax was demonstrated in a clinical endpoint study of 11,404 adult subjects 18 to 49 years of age. Clinical efficacy data are also included in the package inserts for Agriflu, FluMist, and Fluarix. The vaccine efficacy of Flucelvax was similar to those products. Flucelvax was also compared to U.S.-licensed vaccines in two studies; non-inferiority criteria were met in both studies for both adult subjects 18 to 64 years of age and for subjects 65 years of age and older.

The most commonly reported adverse events after influenza vaccines are solicited adverse reactions, particularly pain at the injection site, headache, fatigue, and myalgia. This is consistent with the adverse events reported in the studies of Flucelvax included in this application.

Hypersensitivity reactions, including anaphylaxis, have been reported after influenza vaccination. These reactions have been uncommon. There were no reports of anaphylaxis or serious allergic reactions in this application; however, there was one adverse event of hypersensitivity on the day of vaccination with Flucelvax. This subject received antihistamines and recovered without hospitalization. Another subject reported erythema multiforme after vaccination with Flucelvax; it is possible that this was also an allergic-type of reaction to Flucelvax.

In conclusion, the clinical of Flucelvax and the safety profile were consistent with what has been reported for other approved influenza vaccines.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Flucelvax received regulatory approval initially in the European Union on June 1, 2007 under the tradename, Optaflu™. Only one lot of Optaflu™ has been manufactured and that lot was sold in Germany in the first quarter of 2008. No further doses have been marketed since then. There have been no adverse events reports to the Pharmacovigilance section at Novartis. The applicant has been asked but has not provided a clear explanation regarding the reasons for the limited production of Optaflu for the European market.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

The applicant has conducted US development of Flucelvax under IND 11,580. The first study conducted in the United States was Study V58P5, which was initiated in 2005. CBER convened a Vaccine and Related Biological Products Advisory Committee on November 16, 2005 to review the safety of using MDCK (Madin Darby Canine Kidney Cells) in the manufacture of Flucelvax. At that meeting, the production of Flucelvax in MDCK cells was determined to be

sufficiently safe to support Phase 3 studies of Flucelvax. An End of Phase 2 meeting was held on March 14, 2007. The protocol for Study V58P13 was submitted to IND 11,580 on June 22, 2007. A pre-BLA meeting was held on July 31, 2007. The BLA for Flucelvax was originally submitted in February 2009 but was withdrawn to incorporate the results of the clinical endpoint study. A second pre-BLA meeting was held on December 15, 2010.

This BLA was submitted on November 22, 2011. Subsequent clinical submissions to the BLA include:

- February 28, 2012 – Addendum to Clinical Study Report for Study V58P9 with Novartis audit report of study site and analysis of data omitting the study site in question,
- April 13, 2012 – Lithuanian regulatory authority report on study Site 2 for Study V58P9,
- May 23, 2012 – Response to clinical request about inspections at Site 1 for Study V58P9, and
- August 6, 2012 – Reanalysis of results for Study V58P4 by age subgroups 18-64 years and 65 years and older,
- August 29, 2012 – Summary of safety from Study V58P14 were submitted.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review. However, there were some difficulties with review due to problems with quality control of the application. For example, minor inconsistencies existed between the datasets and the text of Study V58P4. In addition, Study V58P14 was mentioned in the risk management plan, Section 1.1.6 of the BLA, but not in the Clinical Overview, ISS, ISE, or Module 5. Further information for this study was requested. CBER and the applicant agreed that the results from Study V58P4 could be reanalyzed to provide support for Flucelvax use in individuals 65 years of age and older, but an amended study report was not provided and the reanalyzed data were included only in the ISE and ISS, which made the reconciliation of results in the Clinical Study Report and in the ISE and ISS difficult. Finally, no narratives were provided for any subject deaths. In the opinion of this reviewer, the issues with quality did not prevent a thorough review of the safety and efficacy of Flucelvax.

3.2 Compliance With Good Clinical Practices And Submission Integrity

No clinical sites were investigated by FDA for this Biologics License Application. However, during review of the supplement to support traditional approval of Agriflu (BLA 125297, Submission 01), monitors from Bioresearch Monitoring audited three clinical sites of the Study V58P13, which is the primary study to support the efficacy and safety of Flucelvax and was also used to support the traditional approval of Agriflu. These three sites enrolled 15% (N=1705) of subjects in Study V58P13. There was no evidence of underreporting of adverse events, and there were no discrepancies between source data and Case Report Forms or data in the sBLA. In the opinion of the Bioresearch Monitoring Consumer Safety Officer, the inspections did not reveal problems that would impact the data submitted.

During the review of the BLA, the applicant notified CBER of issues with study conduct at one of the two study sites for Study V58P9 on January 26, 2012. Study V58P9 had been conducted

in the 2005 – 2006 influenza season, and the two investigators at Site 2 were arrested in 2007 for fraud and forgery regarding a separate study at their site. These same investigators had conducted Study V58P9 at the same site, and Study V58P9 ended approximately 10 months before the fraudulent study began. The applicant re-audited the study site in March 2007 to examine the potential implications for the results of Study V58P9. Please see the clinical review of Study V58P9 in Section 6.4. The applicant reported conduct at the study site that indicated that Good Clinical Practice was not followed by the investigators during Study V58P9. In addition, this reviewer also has concerns with the study conduct at Site 1. As a result, the results of Study V58P9 were not considered by this reviewer as part of the data to support the safety and efficacy of Flucelvax in this clinical review.

3.3 Financial Disclosures

The applicant provided a synopsis of the Financial Disclosure Regulation to all investigators and requested financial disclosure information from each investigator. Ninety-six percent of investigators responded, and no disclosable financial information was reported. No clinical investigators are or were full or part-time employees of the applicant. In addition, the applicant submitted a completed Form FDA 3454 attesting to the absence of financial interests and arrangements described in 21CFR54.4.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Please see Dr. Gupta's, Dr Murata, and Dr. Ye's reviews.

Dr. Ye reviewed the chemical composition of consecutive lots of Flucelvax and determined that the lots were consistent with each other. Dr. Ye has no concerns with the process being used to manufacture Flucelvax.

Flucelvax is prepared from virus propagated in MDCK cells, a continuous cell line. Live MDCK cells form tumors when inoculated into immunodeficient mice. However, there are no live MDCK cells in the vaccine. The issue of tumorigenicity associated with use of MDCK cells was addressed at an advisory committee meeting on November 16, 2005; at that time, it was determined that the manufacture of a vaccine using MDCK cells do not result in unacceptable risk.

4.2 Assay Validation

Please see Dr. Yan's and Dr. Gupta's reviews.

Dr. Yan states that the pre-specified criteria for statistical analysis of the hemagglutinin inhibition (HAI) assay were met, but that specificity and accuracy were not measured. Therefore, the results are limited by the criteria used.

Assay results when either cell-based or egg-based antigens were used in the HAI assay were compared in Study V58P5. Antibody titers were similar regardless of assay used. Egg-based antigens were used in the assays for the other studies included in this BLA.

The applicant notified CBER in October 2007 of issues with the hemagglutinin inhibition assay used to determine antibody titers to influenza antigens in Studies V58P1, V58P2, V58P4,

V58P4E1, V58P5, and V58P9. During pipetting of serum dilutions in the HAI assay, --(b)(4)---- was aspirated from the wells instead of (b)(4). The sponsor retested serum samples for all studies except Study V58P1, and only retested values were included in the BLA. Since the assays were repeated and pipetting problems would have resulted in lower antibody levels, no bias toward over-estimation of titer values should have been introduced by the problems with pipetting.

4.3 Nonclinical Pharmacology/Toxicology

Nonclinical toxicology data were reviewed by Dr Al-Humadi. The application included the results of a repeated dose toxicology study and a repeated dose reproductive toxicology study. In his review of these studies, Dr. Al-Humadi concluded that there were no test article related safety issues identified.

4.4 Clinical Pharmacology

Not applicable

4.4.1 Mechanism of Action

Vaccination against influenza results in hemagglutination inhibition antibody titers. Specific levels of antibody have been correlated with protection from influenza illness. In some studies, HAI antibody titers of $\geq 1:40$ have been associated with protection from influenza illness in up to 50% of subjects.

4.4.2 Human Pharmacodynamics (PD)

Not applicable

4.4.3 Human Pharmacokinetics (PK)

Not applicable

4.5 Statistical

Please see Dr. Massie's Statistical review.

The Statistical reviewer had concerns with two studies in this BLA. First, the evidence to support the immunogenicity of Flucelvax in the elderly was primarily from Study V58P4. Study V58P4 was not designed to examine the non-inferiority of Flucelvax to a US-licensed influenza vaccine as recommended for an immunogenicity bridging study in, "Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines." In addition, the study population was stratified into two age groups: 18 to 60 years of age and ≥ 61 years of age, which is consistent with the European Medicines Agency's definition of younger adults and elderly but not with the FDA's definition of elderly (≥ 65 years of age). Therefore, both the immunogenicity analyses and the age groups analyzed were conducted post-hoc. Although it is clear that bias may be introduced by post-hoc analyses, CBER agreed to use of the results obtained in the post-hoc analysis; because the study was not originally conducted under US IND, and the study was initiated prior to the publication of the FDA Guidance. In the opinion of CBER medical reviewers, including this reviewer, the possible bias introduced by a post-hoc analysis was minimal since the study was not designed with knowledge of CBER criteria for demonstration of non-inferiority and since the immunogenicity results met the protocol-defined criteria for demonstration of non-inferiority.

In addition, the Statistical review also had concerns about both the post-hoc analysis used and the study conduct of Study V58P9. The study was designed to randomize subjects to receive one of three different lots of Flucelvax, but no criteria for demonstration of lot consistency were included in the study protocol. The study was clearly designed to examine lot consistency, but the criteria for demonstration of lot consistency were only identified after the results of the study were known. In the opinion of this reviewer, this type of post-hoc analysis risks introducing a great deal of bias. The statistical reviewer also had substantial concerns about the conduct of this study; see Section 6.4 of this review. This reviewer agrees that Study V58P9 was not conducted in an appropriate fashion for use of the results in support of the safety or immunogenicity of Flucelvax. There are no federal regulations requiring demonstration of clinical lot consistency prior to vaccine approval, and three consecutive lots were determined by other reviewers to be consistent based on physico-chemical characterization and defined manufacturing specifications.

4.6 Pharmacovigilance

The application was reviewed by Dr. Scott Winiecki of the Division of Epidemiology. The applicant proposed routine pharmacovigilance to monitor potential safety issues. Dr. Winiecki concluded that there were no safety signals for potential safety concerns and that routine pharmacovigilance is an acceptable strategy.

4.7 Advertising and Promotional Labeling Branch

The applicant originally proposed the product name, Optaflu, for the vaccine. There was concern by this reviewer and by Ms. Gallagher and Dr. Stockbridge in the Advertising and Promotional Labeling Branch that the name Optaflu was “fanciful” since “opta” might imply superiority. The applicant subsequently proposed use of the name, Flucelvax, which was approved by the Advertising and Promotional Labeling Branch.

Ms. Gallagher and Dr. Stockbridge were also involved in the review of the package insert for Flucelvax.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

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

5.1 Review Strategy

The applicant submitted seven studies in support of the safety and effectiveness of Flucelvax in persons 18 years of age and older. The primary support of safety and effectiveness is Study V58P13, the clinical endpoint study in 11,404 adults 18 through 49 years of age. The primary support for the safety and effectiveness of Flucelvax in adults 50 years of age and older was Study V58P4. In this study, Flucelvax was compared to a US-licensed vaccine approved for use in that age group using a non-inferiority design. These two studies are reviewed in detail in this clinical review and provide the main support for the effectiveness of Flucelvax in the package insert. The Phase 1 and 2 studies are described more briefly in this review; however, the immunogenicity results for Study V58P5 were highlighted since this was the only study to include HAI results using both cell-derived and egg-derived antigens. Study V58P9 was reviewed in detail because it was the only clinical lot consistency study in the BLA submission. Finally, safety results of all studies were reviewed, particularly for evidence of allergic reactions, for serious adverse events, and for deaths.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The following sections of the BLA were reviewed by this reviewer: Table of Contents, Labeling, Clinical Overview, Integrated Summary of Efficacy, Integrated Summary of Safety, Clinical Study Reports, Case Report Tabulations, Case Report Forms, SAS datasets and Financial Information.

5.3 Table of Studies/Clinical Trials

The number of subjects listed in the table below represents the total number of subjects enrolled in the clinical study included in this BLA, not the number of subjects receiving Flucelvax.

Table 4: Studies for Support of Flucelvax Immunogenicity and Safety

Study	Type	Control	Total # Subjects	Age	Country
Phase 1 and 2 Studies					
V58P1	Phase 1 / 2 observer-blind*, randomized, controlled safety and immunogenicity study	Agriflu	240	≥ 18 years	Germany
V58P2	Phase 2 observer-blind, randomized, controlled safety and immunogenicity study	Agriflu	223	≥ 18 years	New Zealand
V58P5	Phase 2 observer-blind, randomized, controlled, non-inferiority study comparing Flucelvax to Fluvirin	Fluvirin	613	18-49 years	U.S.
Phase 3 Studies					
V58P4	Phase 3 observer-blind, randomized, controlled, non-inferiority study comparing Flucelvax to Agriflu	Agriflu	2654	≥ 18 years	Poland
V58P4E1	Revaccination study for subjects in Study V58P4	Agriflu	2235	≥ 18 years	Poland
V58P9	Phase 3 observer-blind, randomized, controlled, safety, immunogenicity, and lot-to-lot variability study	Agriflu	1200	18-60 years	Lithuania
V58P13	Phase 3, randomized, observer-blind, placebo controlled, clinical endpoint study of Agriflu and Flucelvax with both compared to placebo	Placebo	11404	18-49 years	U.S., Finland, Poland

In the observer blind design, the study personnel who administered the study vaccine was not involved in further safety monitoring or subject follow-up. The study personnel involved in safety monitoring were blinded to identity of the study vaccine.

Source: BLA 125408/0, Clinical Overview, Table 2.5.1.4.1-1, page 12 and text page 12 and Section 5.2, Tabular listing of All Clinical Studies, pages 2-3.

5.4 Consultations

5.4.1 Advisory Committee Meeting

No advisory committee meeting was convened during the current review of this product application. An advisory committee meeting was held in 2005 to discuss the safety of using MDCK cells to manufacture influenza vaccines. See Section 2.5, Regulatory History.

5.4.2 External Consults/Collaborations

There were no external consults or collaborations for this application.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

This Biologics License Application contained the results of three Phase 3 studies and three Phase 1/2 studies.

6.1 Trial #1: Study V58P13 (NCT Number 00630331)

Study Title: Phase 3, randomized, observer-blind, placebo-controlled, multicenter study to assess clinical efficacy of a cell-derived subunit vaccine and an egg-derived subunit vaccine in the 2007-2008 influenza season in healthy adult subjects

6.1.1 Objectives

Flucelvax, an egg-derived influenza vaccine (Agriflu), and placebo were studied in V58P13. The two influenza vaccines were evaluated separately; both were compared to placebo and not to each other. Therefore, study objectives describe the evaluation of both the cell-derived Flucelvax and the egg-derived Agriflu.

The primary objective for this study was to demonstrate protection of the study vaccine (either Flucelvax or Agriflu) compared to placebo against illness caused by virus culture-confirmed community-acquired influenza wild type strains antigenically similar to those contained in the study vaccines.

The secondary objectives were to evaluate:

- protection against illness caused by all virus culture-confirmed community-acquired influenza wild type strains regardless of antigenic match to those contained in the vaccine,
- protection against illness caused by all virus culture-confirmed community-acquired influenza wild type strains dissimilar to those contained in the vaccine,
- protection against illness that does not match the CDC case definition caused by all virus culture-confirmed community-acquired influenza wild type strains that are either antigenically similar, dissimilar, or regardless of antigenic match to those contained in the vaccine,
- reduction in the number of days in bed associated with cases of virus culture-confirmed influenza,
- whether the number of inpatient and outpatient medical visits due to influenza illness or symptoms of influenza was reduced,
- whether the number of days of usual activity (i.e., job, school, household, etc.) lost due to influenza disease was reduced,

- immunogenicity (in a subset of subjects) measured by percentage of subjects who achieved a HAI titer $\geq 1:40$ on Day 22 and by percentage of subjects who achieved seroconversion or ≥ 4 fold rise in titer, and
- safety and tolerability of the study vaccine.

Reviewer comment: Although this study evaluated both Flucelvax and Agriflu, this review focuses on the objectives relating to Flucelvax. Results of this study were also reviewed as part of the clinical review for supplemental BLA 125297, Submission Number 01.

6.1.2 Design Overview

Study V58P13 was a Phase 3 observer-blind, placebo-controlled, multicenter study with planned enrollment of approximately 10,500 subjects aged 18 through 49 years of age. Study subjects were randomized in a 1:1:1 ratio to receive Flucelvax, Agriflu, or placebo (phosphate buffered saline). All subjects received a single 0.5 mL dose of study vaccine intramuscularly in the deltoid muscle of the non-dominant arm. The cell-derived and egg-derived vaccines contained 15 μ g of HA for each of the following strains recommended for the 2007-2008 influenza season in the Northern Hemisphere:

- A/Soloman Islands/3/2006 (H1N1-like),
- A/Wisconsin/67/2005 (H3N2-like), and
- B/Malaysia/ 2506/2004-like.

Subjects were monitored for 30 minutes post-vaccination and then discharged from the study clinic with a Memory Aid. Local and systemic reactogenicity events and all unsolicited adverse events (AEs) were recorded on the Memory Aid from Day 1 to Day 7. Subjects were contacted on Day 8 to collect this information. On Days 8 to 22, subjects were to record all serious AEs, onsets of chronic illnesses, AEs that necessitated a physician consultation and/or lead to study withdrawal, and prescription medications to treat these AEs on the Memory Aid. Subjects were contacted by study personnel on Day 22 to collect this information. From Day 23 to study termination, subjects recorded serious AEs, symptoms meeting the study criteria for evaluation of influenza, and prescription medications used in association with these events. The final study telephone contact was scheduled for approximately 6 months after vaccination; information on adverse events recorded on the Memory Aid was collected at that time. The Memory Aid was not returned to the study center.

The active surveillance period was from November 1, 2007 to April 30, 2008. During this time period, subjects were contacted weekly to remind them of signs and symptoms that would trigger contact of study personnel for influenza culture. If the subject had any two of the following he/she was to be seen by study personnel for laboratory confirmation of influenza: fever/feverish, body aches, cough, sore throat, chills, headache, and runny/snuffy nose. Home visits to obtain nasal and throat specimens for influenza diagnosis were preferred. Attempts were made to collect these specimens within 24 hours of onset, but specimens could be collected up to 72 hours after onset. Specimens were sent to a local laboratory for virus isolation by tissue culture and by PCR. If influenza was isolated, antigenic characterization was performed at a central laboratory.

A subset of subjects enrolled at U.S. study sites were enrolled in an immunogenicity subset. This was to include the first 240 subjects who received Flucelvax, the first 750 subjects who received Agriflu, and the first 60 who received placebo. These subjects had a blood sample obtained pre-vaccination on Day 1 and again on Day 22 for HAI titers.

Reviewer comment: The results of this study provided the primary basis for the assessment of the safety and efficacy of Flucelvax because of the study design (controlled, randomized, and observer-blind with clinical endpoint of prevention of influenza disease) and the large size (more than 11,000 subjects). There was an imbalance in the size of the immunogenicity subsets, because the Applicant used the results of the study to support the size of the database supporting Agriflu immunogenicity, while there were several previously completed studies to support the immunogenicity of Flucelvax.

6.1.3 Population

Study subjects were healthy adult volunteers 18 through 49 years of age.

Subjects were excluded from study participation for any of the following:

- laboratory-confirmed influenza disease within the previous 6 months,
- receipt of an influenza vaccine within 6 months or plans to receive influenza vaccine outside of the study,
- any health condition for which the inactivated influenza vaccine was recommended by the ACIP,
- history of anaphylaxis or serious reaction after administration of any vaccine or hypersensitivity to eggs, egg protein, chicken feathers, influenza viral protein, neomycin, kanamycin, or any vaccine component, chemically related substance, or component of the potential packaging material, such as latex,
- employment in professions prone to influenza transmission to or from high-risk populations or living in the same household as an immunocompromised person,
- history of Guillain-Barre syndrome,
- receipt of an inactivated vaccine within 2 weeks or a live vaccine within 4 weeks,
- acute illness or fever within 3 days,
- any condition that may have interfered with evaluation of the study objectives or the safety of the subject,
- receipt of another investigational agent within 90 days or planned before study completion,
- bleeding diathesis, or
- research staff or family members.

Females who were pregnant or breast-feeding were excluded. Females who were of child bearing potential and were sexually active had to agree to use appropriate birth control methods, as defined in the study protocol.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Study subjects received a single, 0.5 mL dose of study vaccine intramuscularly in the deltoid muscle of the non-dominant arm; study vaccines were Flucelvax (cell-derived vaccine), Agriflu (egg-derived vaccine), or placebo (phosphate buffered saline). Flucelvax and Agriflu contained 15 µg of HA for each of the following strains that were recommended for the 2007-2008 influenza season in the Northern Hemisphere:

- A/Soloman Islands/3/2006 (H1N1-like),
- A/Wisconsin/67/2005 (H3N2-like), and
- Malaysia/ 2506/2004-like.

6.1.5 Sites and Centers

Study V58P13 was conducted at 65 study sites in three countries (United States, Finland, and Poland) with one coordinating investigator in each country.

6.1.6 Surveillance/Monitoring

A medical history and physical examination were performed on all subjects on Day 1, prior to vaccination. Subjects in the immunogenicity subset also had a brief physical examination on Day 22. Subjects remained in clinic for 30 minutes after vaccination to monitor for any immediate reactions. Subjects were discharged with a Memory Aid and instructed to record all AEs and reactogenicity events from Days 1-8; SAEs, AEs that resulted in study withdrawal, and new onset chronic illnesses from Day 1 to study termination; and also to record concomitant medications used to treat these AEs. Subjects were contacted by telephone on Days 8 and 22 and at 6 months post-vaccination for collection of adverse event data. All telephone calls were conducted using a structured telephone interview.

Local reactogenicity events monitored were ecchymosis, erythema, induration, swelling, and pain at the injection site. The severity of local reactogenicity events were graded as none, 1 to ≤ 10 mm, 11 to ≤ 25 mm, 26 to ≤ 50 mm, 51 to ≤ 100 , and > 100 mm. Systemic events followed were chills, malaise, myalgia, arthralgia, headache, sweating, and fatigue. The severity of systemic reactogenicity events and pain at the injection site were categorized as none, mild (transient with no limitation of normal daily activity), moderate (some limitations of activity), and severe (unable to perform normal activity). Subjects were instructed to measure their temperature orally each evening at approximately the same time. Subjects were also to record use of any analgesics or antipyretics for reactogenicity events. Fever was graded as an oral temperature of $\geq 100^\circ\text{F}$ / $\geq 37.8^\circ\text{C}$; severe fever was defined as an oral temperature of $\geq 104^\circ\text{F}$ / $\geq 40^\circ\text{C}$.

All females of child bearing potential were to have a urine pregnancy test prior to vaccination. No other laboratory evaluations were performed.

Any subject who became pregnant in the three weeks following vaccination was followed until delivery, and pregnancy outcome information was collected.

6.1.7 Endpoints and Criteria for Study Success

The primary efficacy endpoint was illness caused by virus culture-confirmed community acquired influenza wild type strains antigenically similar to those contained in the vaccines. The Centers for Disease Control and Prevention (CDC) case definition of influenza-like illness (ILI), which is a fever of $\geq 100^\circ\text{F}$ ($\geq 37.8^\circ\text{C}$) plus cough or sore throat, was used.

Subjects were evaluated for influenza if they reported two of the following signs/symptoms: fever/feverish, body aches, cough, sore throat, chills, headache, and runny/snuffy nose. Nasal and throat specimens were obtained for diagnosis of influenza using tissue culture and PCR. Influenza isolates were evaluated for antigenic characterization.

The immune response to vaccination was measured by pre- and post-vaccination HAI titers to the three influenza strains contained in the vaccine. These were performed at the Clinical Serology Laboratory of Novartis Vaccines in Marburg, Germany. The primary measures of immunogenicity were the percentage of subjects achieving seroconversion, defined as the percentage of subjects with either a pre-vaccination HAI titer $< 1:10$ and a post-vaccination HAI titer $> 1:40$ or ≥ 4 fold increase in HAI antibody titer at Day 22, the percentage of subjects with

HAI titer $\geq 1:40$ at Day 1 and at Day 22, the geometric mean titers (GMTs) at Day 1 and at Day 22, and the Day 22/Day1 geometric mean ratio.

Reviewer comment: CBER usually recommends the use of seroconversion rates and the percentage of subjects with post-vaccination HAI titers of 1:40 or higher as primary immunogenicity endpoints. These two endpoints are described in the FDA Guidance for Industry, “Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines” and were designed for the licensure of trivalent, seasonal influenza vaccines using regulations for accelerated approval. The EMA recommends use of seroconversion rates, the percentage of subjects with post-vaccination HAI titers of 1:40 or higher, and geometric mean ratios for evaluation of immunogenicity in yearly registration studies.

6.1.8 Statistical Considerations & Statistical Analysis Plan

Study subjects were randomized using the Novartis Vaccines Biostatistics and Statistical Reporting system. The study was observer-blind. Designated study personnel, who administered the study vaccine, were not involved in study monitoring or conduct and had no further contact with the study subject. Study personnel recording observations were blinded to treatment assignments.

The primary analysis evaluated protection against illness caused by virus culture-confirmed, community acquired influenza wild type strains antigenically similar to those contained in the vaccines. Vaccine efficacy would be demonstrated if the lower bound, one-sided 97.5% CI for vaccine efficacy was greater than 40%.

The populations analyzed included:

- All enrolled population defined as all subjects who had demographic data available,
- Full analysis set/Modified intention-to-treat (MITT) population defined as all subjects in the enrolled population who received the study vaccine,
- Immunogenicity population defined as all subjects in the enrolled population who received the study vaccine and provided at least one evaluable serum sample before and after baseline,
- Per protocol (PP) population defined as subjects in the modified intention-to-treat population who received the correct dose of the vaccine and had no major protocol violation prior to unblinding (a major protocol violation is one that is considered to have a significant impact on results),
- Exposed population defined as all subjects who received a study vaccination, and
- Safety population defined as all subjects in the exposed population who provide post-vaccination safety data.

Differences between vaccine groups in seroconversion rates or percentage of subjects with HAI titers $\geq 1:40$ were compared using the chi-square test. GMTs with their associated 95% confidence intervals were also calculated for each antigen and each vaccine group. Vaccine group differences were assessed using ANOVA. The geometric mean ratio was calculated for each antigen and each vaccine group along with the associated 95% confidence interval. Geometric mean ratios were compared between treatment groups using ANOVA statistical testing.

Adverse events were categorized using MedDRA terms. All reactogenicity events and AEs were to be summarized and compared between arms using Pearson's chi-square test or Fisher's Exact test.

A total of 10,500 subjects were to be enrolled with an expected drop out rate of 10% resulting in at least 9450 evaluable subjects. Vaccine efficacy for both vaccines was estimated at 70%, and influenza attack rate was estimated to be 3%, resulting in a 0.94 probability that the lower limits of the one-sided 97.5% confidence intervals for efficacy would be greater than 40%. The study was powered to demonstrate the efficacy of each vaccine individually and was not powered to compare the two vaccines. Because the two vaccines were evaluated separately, no alpha-adjustment was made.

6.1.9 Results

6.1.9.1 Study Population and Disposition

Study V58P13 was conducted at 65 study sites in three countries (United States, Finland, and Poland) with one coordinating investigator in each country. The first study subject was enrolled on October 9, 2007 and the last subject completed the study on July 8, 2008.

6.1.9.1.1 Populations Enrolled/Analyzed and Subject Disposition

A total of 11,404 subjects were enrolled and randomized: 3823 in the Flucelvax arm, 3676 in the Agriflu arm, and 3900 in the placebo arm. Of these subjects, 11,299 were vaccinated, and 10,844 completed the study. See the following table for a summary of study subject disposition.

Table 5: Study V58P13 - Subject Disposition

	Flucelvax	Agriflu	Placebo
Enrolled	3828	3676	3900
Vaccinated	3818	3668	3896
Completed study	3622 (95%)	3510 (95%)	3712 (95%)
Premature discontinuations	206 (5%)	166 (5%)	188 (5%)
Death	2	1	1
Adverse event	1	0	0
Consent withdrawn	12	7	5
Lost to follow-up	175	143	170
Inappropriate enrollment	3	6	3
Protocol deviation/violation	4	5	6
Unknown to classify	9	4	3

Source: BLA 125408/0, CSR for V58P13, Table 10.1-1, page 57

Ninety-five percent of subjects in each study arm completed the study. The majority of premature study discontinuations in each study arm (85-90%) were due to loss to follow-up. There were five premature discontinuations due to death and one due to an adverse event; see Sections 6.1.12.2 and 6.1.12.3 for discussions of these six subjects. The majority of study discontinuations in each arm were after Day 21 and prior to study completion.

Reviewer comment: The percentage of subjects (5%) with premature discontinuation was relatively small and was the same in each study arm. In addition, the majority of premature discontinuations were due to loss to follow-up during a long follow-up period. Therefore, it appears that study follow-up procedures were in a range that is unlikely to have affected the validity of study results.

Protocol deviations

Protocol violations were reported in 1584 subjects: 526 in the Flucelvax arm, 503 in the Agriflu arm, and 555 in the placebo arm. The two most common protocol deviations were visit outside of the protocol-defined window for Visit 3, which was observed in 46% of subjects with a protocol deviation in the Flucelvax arm, 49.5% in the Agriflu arm, and 49% in the placebo arm, and loss to follow-up, which was observed in 33% of subjects with a protocol deviation in the Flucelvax arm, 28% in the Agriflu arm, and 31% in the placebo arm. Other protocol deviations were observed in 5% of subjects or fewer. Lack of serum sample at Visit 3 and serum sample outside of window at Visit 3 were observed more often in the Agriflu arm (4.2% and 5.0% respectively) than in the Flucelvax arm (0.95% and 1.1%) and the placebo arm (0.54% and 0.36%). The percentage of subjects with other protocol deviations was similar between the study arms.

Reviewer comment: Subjects with Visit 3 (Day 22) outside of the protocol defined window of -1 to +3 days accounted for almost one-half of subjects with protocol deviations. However, when the percentage of subjects with Visit 3 outside of the protocol-defined window was calculated for the entire study arm, instead of for the subgroup of subjects with a protocol deviation, 6.4% of all Flucelvax subjects were lost to follow up, 6.8% of all Agriflu subjects were lost to follow up, and 7.1% of all placebo subjects were lost to follow up. This percentage of the total study population is unlikely to have affected the study results. In addition, in the applicant's discussion of exclusions from the Per Protocol Population, the majority of these were not major violations and were unlikely to have impacted study results.

Seventy-one subjects were excluded from the Per Protocol Population due to major protocol deviations. The reasons for exclusion from the Per Protocol Populations are shown in the following table.

Table 6: Study V58P13 - Number of Subjects Excluded from the Per Protocol Population and Reasons for Exclusion

	Flucelvax N=11	Agriflu N=54	Placebo N=6
Visit 3 blood draw outside window	6	25	2
No post-baseline Ab data	5	21	3
No visit 3 serum sample	5	21	3
Randomized, not vaccinated	0	4	1
Entry criteria not met	0	3	1
Received excluded medication	0	2	0
Received wrong treatment	0	2	0
Visit 1 blood draw outside window	0	1	0

Source: BLA 125408/0, CSR for V58P13, Table 10.2-2, page 64

Reviewer comment: The number of subjects excluded from the Per Protocol Population was much higher in the Agriflu arm compared to the Flucelvax and placebo arms. Only three reasons for exclusion from the PP population in the Flucelvax arm were noted: visit 3 outside of window (N=6), no post-vaccination antibody titer (N=5), and no visit 3 (N=5). It is unclear how visit 3 outside the 3 window would have affected the clinical endpoint (prevention of influenza disease); however, the overall percentage of Flucelvax recipients excluded from the Per Protocol Population was low ($\leq 1.5\%$) and unlikely to affect study conclusions

The differences in the Per Protocol Population and the Modified Intent-to-Treat (MITT) Populations for efficacy and for immunogenicity are shown in the table below. In the efficacy analysis, the MITT included all subjects vaccinated; reasons for exclusion from the Per Protocol Population are shown in the previous table. The MITT population for immunogenicity included subjects who were vaccinated and provided at least one evaluable serum sample before and/or after baseline. The Per Protocol immunogenicity population included subjects who had correctly received the study vaccine, provided evaluable serum samples during the protocol-defined window, and had no major protocol deviations.

Table 7: Study V58P13 - Number of Subjects in the Per Protocol (PP) Population and the Modified Intent-to-Treat (MITT) Population for Analysis of Efficacy and of Immunogenicity

	Flucelvax	Agriflu	Placebo
Efficacy			
PP	3776	3638	3843
MITT	3790	3648	3861
Immunogenicity			
PP	228	695	55
MITT	235	722	58

Source: BLA 125408/0, CSR for V58P13, Text, pages 64-65

Reviewer comment: The differences between the MITT and PP populations were small. Therefore, the PP populations were appropriate populations for analysis of efficacy and immunogenicity.

6.1.9.1.2 Demographics

The majority of study subjects were female (55%) and Caucasian (84%). Fourteen percent had received a seasonal influenza vaccine the previous year. Demographic and baseline characteristics of each study arm are shown in the table below.

Table 8: Study V58P13 - Demographic and Baseline Characteristics for Total Enrolled Population

	Flucelvax N=3828	Agriflu N=3676	Placebo N=3900
Gender			
Female	2088 (55%)	2026 (55%)	2176 (56%)
Race			
Caucasian	3228 (84%)	3107 (85%)	3301 (85%)
Hispanic	295 (8%)	276 (8%)	272 (7%)
Black	262 (7%)	247 (7%)	289 (7%)
Asian	24 (<1%)	24 (<1%)	24 (<1%)
Native American/ Alaskan	2 (<1%)	3 (<1%)	5 (<1%)
Pacific Islander / Hawaiian	6 (<1%)	3 (<1%)	1 (<1%)
Other	11 (<1%)	15 (<1%)	6 (<1%)
Not Available	0	1	2
Vaccinated in Previous Year	556 (15%)	511 (14%)	524 (13%)

Source: BLA 125408/0, CSR for V58P13, Table 11.2-1, page 67

Reviewer comment: As shown in the table above, the demographics and baseline characteristics were similar in the three study arms. The racial and ethnic demographics are acceptably similar to US demographics, according to the US Census Bureau statistics for 2008 (www.factfinder.census.gov).

Demographic and baseline characteristics were also provided for the immunogenicity subset. In the immunogenicity subset, 58% of subjects were female. This subset included more Hispanics (20%) and Blacks (11%) and fewer Caucasians (67%) than the Total Enrolled Population. The percentage of subjects who had been vaccinated in the previous year was higher (22%) than in the Total Enrolled Population.

Reviewer comment: The demographic and baseline characteristics were slightly different in the immunogenicity subset compared to the Total Enrolled Populations. Although there was a higher percentage of Hispanics and Blacks in the immunogenicity subset; there is no known difference in antibody response to influenza vaccine by race or ethnicity, so the antibody response in the immunogenicity subset should be consistent with what would be expected in the total population. The percentage of subjects, who had been vaccinated in the previous year, was higher in the immunogenicity subset. This may have resulted in lower seroconversion rates and higher baseline and post-vaccination

percentages of subjects with post-vaccination titers of 1:40 or higher. Please see immunogenicity results discussed later in this review.

6.1.10 Efficacy Analyses

6.1.10.1 Analyses of Primary Endpoint(s)

The primary objective was to demonstrate protection of the study vaccine (either Flucelvax or Agriflu) compared to placebo against illness caused by culture-confirmed, community-acquired influenza wild type strains antigenically similar to those contained in the study vaccine. Vaccine efficacy would be demonstrated if the lower-bound one-sided 97.5% confidence interval for vaccine efficacy was greater than 40%. Results for the primary endpoint are shown in the table below.

Table 9: Study V58P13 - Point Estimate and One-Sided 97.5% Confidence Interval (CI) for Vaccine Efficacy against Vaccine Matched Influenza Strains (Per Protocol Efficacy Population)

	Total # subjects	# Subjects with Influenza	Attack Rate	Vaccine Efficacy (vs. Placebo)	97.5% CI*
Flucelvax	3776	7	0.19%	83.8%	61.0
Agriflu	3638	9	0.25%	78.4%	52.1
Placebo	3843	44	1.14%	--	--

Source: BLA 125408/0, CSR for V58P13, Table 11.4.1.1.1-1, page 73

As shown in the table above, the lower bound one-sided 97.5% CI for vaccine efficacy was 61% for Flucelvax and 52.1% for Agriflu. The results for both vaccines met the protocol-defined criteria for demonstration of efficacy.

6.1.10.2 Analyses of Secondary Endpoints

Vaccine efficacy against vaccine-mismatched influenza virus strains (i.e., influenza strains isolated from subjects during the study that are not closely related to influenza virus strains included in the study vaccines) is shown in the table below.

Table 10: Study V58P13 - Point Estimate and One-Sided 97.5% Confidence Interval (CI) for Vaccine Efficacy against Vaccine-Mismatched Influenza Strains (Per Protocol Efficacy Population)

	Total # subjects	# Subjects with Influenza	Attack Rate	Vaccine Efficacy (vs. Placebo)	97.5% CI*
Flucelvax	3776	25	0.79%	58.7%	33.5%
Agriflu	3638	29	0.8%	58.6%	32.9%
Placebo	3843	74	1.93%	--	--

*97.5%CI=lower bound of one-sided 97.5% confidence interval

Source: BLA 125408/0, CSR for V58P13, Table 11.4.1.1.2-1, page 74

Reviewer comment: While the lower bound one-sided 97.5% CI did not meet the protocol-defined criteria for demonstration of efficacy for vaccine-matched strains, the results do provide evidence of protection against influenza strains that were not included in the vaccine.

Results for vaccine efficacy against all influenza strains, vaccine matched and mismatched, are shown in the table below.

Table 11: Study V58P13 - Point Estimate and One-Sided 97.5% Confidence Interval (CI) for Vaccine Efficacy against Vaccine Matched and Mismatched Influenza Strains (Per Protocol Efficacy Population)

	Total # subjects	# Subjects with Influenza	Attack Rate	Vaccine Efficacy (vs. Placebo)	LB 95% CI*
Flucelvax	3776	42	1.1%	69.5%	55.0
Agriflu	3638	49	1.35%	63%	46.7
Placebo	3843	140	3.6%	--	--

*97.5%CI=lower bound of one-sided 97.5% confidence interval

Source: BLA 125408/0, CSR for V58P13, Table 11.4.1.1.2-2, page 75

Reviewer comment: Efficacy against all influenza strains may best represent the efficacy of the vaccine in actual use. Vaccine efficacy against all influenza strains met the same criteria used for demonstration of efficacy against matched strains for both Flucelvax and Agriflu.

Results for vaccine efficacy against each vaccine strain for both matched influenza strains and all influenza strains are shown in the table below.

Table 12: Study V58P13 - Vaccine Efficacy by Vaccine Strain against Vaccine Matched Influenza Strains (Per Protocol Efficacy Population)

	Flucelvax Attack Rate	Flucelvax Number of Subjects with Influenza/Total	Placebo Attack Rate	Placebo Number of Subjects with Influenza/Total	Point Estimate for Vaccine Efficacy	97.5% CI for Vaccine Efficacy*
Antigenically Matched Strains						
A/H3N2	0.05%	7/3776	0	0/3843	N/E [^]	N/E
A/H1N1	0.13%	5/3776	1.12%	43/3843	88.2%	67.4%
B [#]	0	0	0.03%	1/3843	N/E	N/E
All Culture-Confirmed Influenza						
A/H3N2	0.16%	6/3776	0.65%	25/3843	75.6%	35.1%
A/H1N1	0.16%	6/3776	1.48%	57/3843	89.3%	73.0%
B	0.79%	30/3776	1.59%	61/3843	49.9%	18.2%

*97.5% CI=lower bound of one-sided 97.5% confidence interval

[^]N/E = Not Evaluable

[#]Too few cases of influenza due to vaccine-matched influenza B to adequately assess vaccine efficacy.

Source: BLA 125408/0, CSR for V58P13, Tables 11.4.1.1.1-1 and 11.4.1.1.2-2, pages 73 and 75

Reviewer comment: As shown in the previous table, vaccine efficacy for vaccine-matched strains was largely driven by the results for the H1N1 strain. Seven H3N2 isolates and one B isolate matched the vaccine strains. When all strains, matched and mismatched were analyzed, all three influenza viruses were isolated: 31 H3N2 isolates, 63 H1N1 isolates, and 91 B isolates. Vaccine efficacy for Flucelvax against individual *matched* strains was demonstrated for A/H1N1 strains only. Too few matched influenza B isolates were isolated to reach any conclusion about efficacy, and it is difficult to determine efficacy against matched A/H3N2 strains since there were no matched A/H3N2 strains isolated in the placebo arm and only 7 in the Flucelvax arm. However, on analysis of vaccine efficacy against *all* strains, matched and unmatched, efficacy was demonstrated with the point estimates greater than 40% for H1N1, H3N2, and B viruses. The one-sided confidence intervals were lower for the A/H3N2 and B strains, which may have been related, in part, to the smaller numbers used in these analyses. Of note, the majority of influenza disease was due to influenza subtype A/H1N1; however, this was not the pandemic H1N1 2009 influenza subtype.

Number of days in bed, the number of inpatient and outpatient medical visits, and number of days of usual activity were analyzed as secondary endpoints. No meaningful differences in the incidences of any of these outcomes were observed in the Flucelvax and placebo arms on analysis using the population of Per Protocol subjects with culture-confirmed influenza. However, the results were statistically significant for the entire Per Protocol Population with an ILI, regardless of virus culture results.

Table 13: Study V58P13 - Influenza or ILI-Associated Days in Bed, Number of Medical Visits, and Days of Usual Activity Lost By Study Population

	Flucelvax	Agriflu	Placebo
<i>Per Protocol Population, Influenza Culture-Positive Subset</i>			
Mean Days in Bed	3.9	2.9	3.4
Mean Number of Medical Visits	0.8	0.6	0.8
Mean Number of Days of Usual Activity Lost	5.1	4.0	4.6
<i>Entire Per Protocol Population (ILI)</i>			
Mean Days in Bed	0.04	0.04	0.12
Mean Number of Medical Visits	0.01	0.01	0.03
Mean Number of Days of Usual Activity Lost	0.06	0.05	0.16

Source: BLA 125408/0, CSR for V58P13, Tables 11.4.1.1.2-3 and 11.4.1.1.2-4, page 77

Reviewer comments: The analysis of days in bed, number of medical visits, and number of days of usual activity lost may be interpreted as an analysis of endpoints that are consistent with milder clinical influenza. According to this interpretation, no difference in milder clinical influenza disease in Flucelvax vaccinated subjects compared to placebo subjects was observed. Although vaccine efficacy was slightly higher in the Flucelvax arm than the Agriflu arm, the mean number of days in bed, number of medical visits, and number of days of usual activity lost were actually higher in the Flucelvax arm. These findings suggest that clinical disease due to influenza was not similar for subjects who were vaccinated with Flucelvax and those who received placebo. This suggests that vaccination with Flucelvax prevented clinical influenza disease but did not decrease disease severity in subjects who were vaccinated and developed influenza. In the analysis of the PP population of subjects with an ILI, significant decreases in the number of days in bed, number of medical visits, and number of days of usual activity lost were observed in the Flucelvax arm compared to placebo. However, subjects with ILI may represent subjects with culture-positive influenza disease, subjects with influenza and negative cultures, and subjects with clinical disease due to other pathogens. While much of the difference between Flucelvax and placebo was likely due to the decrease in clinical influenza disease after vaccination with Flucelvax, the contribution of other factors in this analysis is unclear. Overall, a biological mechanism for these decreases in such a heterogeneous population is not readily apparent.

Vaccine efficacy was also analyzed for the Modified Intent-to-Treat (MITT) population and is shown for vaccine-matched influenza virus strains in the following table.

Table 14: Study V58P13 - Point Estimate and One-Sided 97.5% Confidence Interval (CI) for Vaccine Efficacy against Vaccine Matched Influenza Strains (MITT) Population)

	Total # subjects	# Subjects with Influenza	Attack Rate	Vaccine Efficacy (vs. Placebo)	97.5% CI*
Flucelvax	3790	7	0.18%	83.8%	60.9%
Agriflu	3648	9	0.25%	78.4%	52.0%
Placebo	3861	44	1.14%	--	--

Source: BLA 125408/0, CSR for V58P13, Table 14.2.1.1.1, page 142

Vaccine efficacy estimates were similar for the MITT population as for the Per Protocol population. These results met the protocol-defined criteria for demonstration of vaccine efficacy used in the Per Protocol analysis.

6.1.10.2 Immunogenicity subset

Serum anti-HAI antibody levels were measured as a secondary endpoint. Antibody levels were assessed using seroconversion rates, percentage of subjects with post-vaccination HAI titers of 1:40 or greater, the geometric mean titers (GMTs) at Days 1 and 22, and the Day 22 to Day 1 geometric mean ratio. The study protocol-defined criteria for demonstration of immunogenicity were:

- Lower bound of the 95% CI for the percentage of subjects with post-vaccination HAI titers $\geq 1:40$ of $\geq 70\%$, and
- Lower bound of the 95% CI for seroconversion rate of $\geq 40\%$.

These criteria needed to be met for each influenza strain in the vaccine.

Reviewer comment: These criteria for demonstration of immunogenicity are described in the FDA Guidance for Industry, “Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines” and were intended for the licensure of trivalent, seasonal influenza vaccines using regulations for accelerated approval.

Immunogenicity results are shown in the following tables.

Table 15: Study V58P13 - Percentage of Subjects with HAI Seroconversion Rate and HAI Titers of 1:40 or Greater, Per Protocol Immunogenicity Population

	Flucelvax N=228			Agriflu N=695			Placebo N=55		
	H3N2	H1N1	B	H3N2	H1N1	B	H3N2	H1N1	B
<i>Seroconversion Rates</i>									
SCR	59%	78%	51%	68%	75%	68%	0	0	0
LB 95% CI	53%	72%	45%	64%	71%	65%	0	0	0
<i>Percentage of Subjects with HAI Titers \geq 1:40</i>									
% \geq 1:40 Baseline	63%	48%	25%	58%	53%	23%	71%	60%	22%
% \geq 1:40 Day 22	99%	99%	78%	99%	98%	92%	65%	60%	22%
LB 95% CI	98%	97%	72%	98%	97%	72%	51%	46%	12%

Source: BLA 125408/0, CSR for V58P13, Tables 11.4.1.2-1, page 81

Reviewer comment: As discussed earlier in this review, 14% of subjects had received an influenza vaccination in the previous year. The baseline percentage of subjects with HAI titers \geq 1:40 to the two influenza A subtypes was relatively high with 48% of all subjects or more having HAI titers \geq 1:40. The baseline percentage of subjects with HAI titers of 1:40 or higher to the influenza B vaccine strain was lower and ranged from 22 to 25% in the three study arms. Although the percentage of subjects with baseline HAI titers of 1:40 or greater to the influenza B strain were similar in each arm, the percentage of subjects with baseline HAI titers \geq 1:40 to H3N2 ranged from 58% to 71% and to H1N1 ranged from 48% to 60%. The percentage of subjects with baseline HAI titers \geq 1:40 to the influenza A viruses was higher in the placebo arm and was unlikely to have biased the clinical endpoint results in favor of Flucelvax.

The lower bound 95% confidence interval for the seroconversion rate was greater than 40% for all three strains in both the Flucelvax and the Agriflu arms, but was zero for all three strains in the placebo arm. The percentage of subjects with post-vaccination HAI titers of 1:40 or higher was greater than 70% for all three vaccine strains in the Flucelvax arm, but not in the placebo arm. These results met the protocol-defined criteria for demonstration of immunogenicity.

Reviewer comment: Four fold rises in HAI titers after vaccination were relatively common in spite of the high percentage of subjects with baseline HAI titers of 1:40 or higher.

**Table 16: Study V58P13 - Geometric Mean Titers (GMTs) Pre- and Post-Vaccination
Per Protocol Immunogenicity Population**

	Flucelvax N=228			Agriflu N=695			Placebo N=55		
	H3N2	H1N1	B	H3N2	H1N1	B	H3N2	H1N1	B
GMT Baseline	48	34	14	41	35	13	56	37	12
GMT Day 22	332	566	72	357	499	120	53	36	12

Source: BLA 125408/0, CSR for V58P13, Tables 11.4.1.2-1, page 81

Only nine subjects in the immunogenicity subset; all in the Agriflu arm, had culture-confirmed influenza. Four of these were due to vaccine mismatched influenza B and five by non-characterizable A/H3N2 strains.

Reviewer comment: The applicant noted that too few culture-confirmed cases of influenza were observed in the immunogenicity subset to reach any conclusions regarding a correlation of HAI antibody responses with efficacy. This reviewer agrees.

6.1.10.3 Subpopulation Analyses

Subgroup analyses were provided by region, previous vaccination, sex, and ethnicity. The results for subjects enrolled in the United States compared to those enrolled in Europe are shown in the table below.

Table 17: Study V58P13 - Point Estimates for Vaccine Efficacy by Vaccine-Matched Influenza and All Vaccine Strains (Matched and Mismatched) and by Region

	Matched Strains		All Strains	
	United States	Europe	United States	Europe
Flucelvax	-3.8	88.1	68.3	70.1
Agriflu	43.0	81.0	43.0	70.3

Source: BLA 125408/0, CSR for V58P13, Table 11.4.2.8-1, page 85-86

Results by region (United States and Europe) were influenced by the predominant circulating influenza strains. The primary strains circulating during the study period were influenza A/H3N2 in the United States and A/H1N1 in Europe. Both influenza A subtypes were similar to those contained in the vaccine. Influenza B strains that circulated in the US and Europe during the time of the study were not similar to the B strain in the vaccine. In addition, only a small number of cases of influenza were in the United States: 2 confirmed cases of influenza disease due to matched strains in the placebo group, two in the Flucelvax group and one in the Agriflu group,

Reviewer comment: On further review of data tables 14.2.1.1 and 14.2.1.3, the overwhelming majority of subjects with disease due to culture-confirmed influenza were in Europe. The number of subjects in the United States and

Europe with culture-confirmed influenza is shown in the table below. Note that this table differs from other tables in that the cases are divided into matched strains and mismatched strains and the results for all strains are not included.

Table 18: Study V58P13 - Number of Subjects with Culture-Confirmed Influenza by Region

	Matched Strains		Vaccine Mismatched Strains	
	United States	Europe	United States	Europe
Flucelvax	2	5	11	31
Agriflu	1	8	18	31
Placebo	2	42	36	104
Total	5	55	65	166

Source: BLA 125408/0, CSR for V58P13, Tables 14.2.1.1 and 14.2.1.2, pages 141 and 143

There were 55 subjects in Europe with influenza due to vaccine-matched strains compared to only 5 in the US, and there were 166 subjects in Europe with influenza due to any strain compared to 65 in the US. As stated previously in this review, results of this study are largely driven by influenza A/H1N1, which was circulating in Europe during the study; therefore, vaccine efficacy is largely based on the results from European sites.

Reviewer comment: In the opinion of this reviewer, the data support vaccine efficacy in the United States because 1) the point estimate for Flucelvax vaccine efficacy in the United States was 68.3% for all strains and 2) there is no evidence that the efficacy of influenza vaccines differs by race or ethnicity. In addition, the study was not designed or powered to demonstrate vaccine efficacy by country of origin subgroup.

The percentage of subjects who had been vaccinated against influenza in the previous year was small: 15% in the Flucelvax arm, 14% in the Agriflu arm, and 13% in the placebo arm. Results for vaccine efficacy by receipt of influenza vaccine in the previous year are shown in the table below.

Table 19: Study V58P13 – Number of Subjects with Influenza (Point Estimates for Vaccine Efficacy) by Vaccine-Matched Influenza and All Vaccine Strains (Matched and Mismatched) and by Prior Year Vaccination

	Matched Strains		All Strains	
	Vaccinated	Not Vaccinated	Vaccinated	Not Vaccinated
Flucelvax	0 (100%)	6 (84.0%)	7 (64.9%)	33 (70.7%)
Agriflu	1 (74.3%)	7 (81.1%)	5 (72.9%)	34 (69.4%)

Source: BLA 125408/0, CSR for V58P13, Table 11.4.2.8-1, page 85-86

Reviewer comment: The number of subjects with culture-confirmed influenza disease in the subgroup who had previously been vaccinated was small. Influenza disease due to a vaccine matched strain in previously vaccinated subjects was not observed in Flucelvax recipients. Influenza disease due to vaccine mismatched strains in subjects who had previously been vaccinated was reported in five subjects in the Flucelvax arm, three subjects in the Agriflu arm, and ten subjects in the placebo arm. Although the number of

subjects with culture-confirmed influenza disease was lower in subjects who had been vaccinated in the previous year, the denominator of total number of subjects who had been previously vaccinated was also smaller, and the point estimate for vaccine efficacy was greater than 69% in each subgroup and arm.

Vaccine efficacy results by gender are shown in the following table.

Table 20: Study V58P13 - Point Estimates for Vaccine Efficacy by Vaccine-Matched Influenza and All Vaccine Strains (Matched and Mismatched) and by Gender

	Matched Strains		Mismatched Strains	
	Female	Male	Female	Male
Flucelvax	80.2%	87.1%	72.8%	64.6%
Agriflu	79.7%	77.4%	63.1%	62.8%

Source: BLA 125408/0, CSR for V58P13, Table 11.4.2.8-1, page 85-86

Reviewer comment: In the Flucelvax arm, vaccine efficacy was slightly higher for males for matched strains and slightly higher for females in mismatched strains. These differences are small and unlikely to be of clinical significance. In addition, the point estimate for vaccine efficacy for all subgroups was higher than 63%.

Vaccine efficacy by race is shown in the table below. Because the majority of subjects were Caucasian (84-85% of each arm) and the percentage of other races was small, the analysis compared Caucasians and non-Caucasians.

Table 21: Study V58P13 - Point Estimates for Vaccine Efficacy by Vaccine-Matched Influenza and All Vaccine Strains (Matched and Mismatched) and by Race

	Matched Strains		Mismatched Strains	
	Caucasian	Non-Caucasian	Caucasian	Non-Caucasian
Flucelvax	86.1%	Not done	69.0%	80.1%
Agriflu	78.3%	Not done	63.9%	37.9%

Source: BLA 125408/0, CSR for V58P13, Table 11.4.2.8-1, page 85-86

Reviewer comment: Point estimates of efficacy by race were likely derived from small numbers of non-Caucasians and the small number of cases of influenza in non-Caucasians. The number of subjects with culture-confirmed influenza by race is shown in the table below.

Table 22: Study V58P13 - Number of Subjects with Culture-Confirmed Influenza by Race

	Matched Strains		Vaccine Mismatched Strains	
	Caucasian	Non-Caucasian	Caucasian	Non-Caucasian
Flucelvax	0	1	30	0
Agriflu	9	0	27	2
Placebo	44	0	70	4
Total	53	1	127	6

Source: BLA 125408/0, CSR for V58P13, Tables 14.2.1.1 and 14.2.1.2, pages 141 and 143

Reviewer comment: Because of the small number of cases of influenza in the non-Caucasian subgroup, it is difficult to reach any conclusions regarding differences in efficacy by race.

6.1.11 Safety Analyses

6.1.11.1 Safety Population

A total of 11404 subjects were enrolled, and 11376 were included in the safety population (3813 in the Flucelvax arm, 3669 in the Agriflu arm, and 3894 in the placebo arm). The safety population consisted of all subjects who were randomized and provided post-vaccination safety data.

Twenty-eight subjects were excluded from the safety population: 11 from the Flucelvax arm, 10 from the Agriflu arm, and 7 from the placebo arm. The reasons for exclusion from the safety population were:

- Flucelvax arm – 10 randomized but not vaccinated, 1 randomized and vaccinated at two different study sites,
- Agriflu arm – 7 randomized but not vaccinated, 3 vaccinated but no post-vaccination safety records and
- Placebo arm – 4 randomized but not vaccinated, 2 vaccinated but no post-vaccination safety record, and 1 randomized and vaccinated at two different study sites.

Reviewer comment: The number of subjects excluded from the safety population was small and should not affect conclusions of the safety analysis.

6.1.11.2 Non-Serious Adverse Events

Solicited adverse reactions

Solicited adverse reactions were followed for the seven days after vaccination. The percentages of subjects reporting solicited adverse reactions are shown in the table below.

Table 23: Study V58P13 - Percentage of Subjects with Solicited Adverse Reactions

	Flucelvax N=3813	Agriflu N=3669	Placebo N=3894
Any	53%	49%	39%
Local	40%	35%	21%
Systemic	30%	28%	25%
Other*	11%	12%	10%

*Other is the percentage of subjects who stayed home due to solicited reactions and the percentage of subjects who used analgesic/antipyretic medication
Source: BLA 125408/0, CSR for V58P13, Table 12.2.1.1-1, page 94

The percentage of subjects with any adverse reactions and with local adverse reactions was substantially higher in the Flucelvax arm compared to the placebo arm. There was also a higher percentage of subjects reporting any solicited adverse reaction in the Flucelvax arm compared to the Agriflu arm. The incidence of the individual local solicited reactions is shown in the following table. There were no severe reactions reported for induration, ecchymosis, or swelling, so these categories are not included in the table.

Table 24: Study V58P13 - Percentage of Subjects Reporting Individual Local Solicited Adverse Reactions

	Flucelvax N=3813	Agriflu N=3669	Placebo N=3894
Pain			
Any	30%	24%	10%
Severe	<1%	<1%	<1%
Erythema			
Any	13%	13%	10%
> 100 mm	0	<1%	<1%
Induration	6%	6%	3%
Ecchymosis	3%	3%	4%
Swelling	6%	5%	3%

Source: BLA 125408/0, CSR for V58P13, Table 12.2.3-1, page 98

Pain was the most frequently reported solicited local adverse reaction and was observed in 30% of Flucelvax recipients and in 24% of Agriflu recipients compared to 10% of placebo recipients. The only other solicited local adverse reaction observed in more than 10% of subjects was erythema, which was reported in 13% of both Flucelvax and Agriflu recipients and in slightly fewer placebo recipients (10%).

Severe pain was reported in less than 1% of subjects in all study groups; the number of subjects with severe pain was higher in the Flucelvax arm (N=13) compared to the Agriflu arm (N=4) and the placebo arm (N=3). Severe erythema (>100 mm) was not reported in the Flucelvax arm but was reported in two Agriflu recipients and one placebo recipient.

In the Flucelvax and Agriflu arms, the highest percentage of subjects with pain or erythema was observed on Day 1 of the study. The percentage with induration was highest on Day 2 in both arms. The incidence of subjects with ecchymosis peaked on Day 2 in the Flucelvax arm. The percentage with ecchymosis was similar in the Agriflu arm from Days 1 through 4. Similar percentages of swelling were observed in the first two to three days in the Agriflu and Flucelvax arms. The percentage of subjects with individual local reactions after Day 7 was <1% for each adverse reaction in each study arm.

Reviewer comment: Pain at the injection site was common after Flucelvax and Agriflu vaccination and was reported in almost one-fourth of subjects. Erythema was reported in 13% of Flucelvax recipients and all other solicited local adverse reactions were reported in less than 10% of subjects. Although the incidence of solicited local adverse reactions was higher in the Flucelvax and Agriflu arms for all reactions except ecchymosis, the differences were small for all reactions except pain. Severe solicited local adverse reactions were uncommon. Most reactions were reported on the day of vaccination or the following day.

The percentages of subjects with individual solicited systemic adverse reactions are shown in the following table.

Table 25: Study V58P13 - Percentage of Subjects Reporting Individual Systemic Solicited Adverse Reactions

	Flucelvax N=3813	Agriflu N=3669	Placebo N=3894
Chills			
Any	6%	6%	6%
Severe	<1%	<1%	<1%
Malaise			
Any	8%	7%	6%
Severe	<1%	<1%	1%
Myalgia			
Any	12%	10%	7%
Severe	<1%	<1%	<1%
Arthralgia			
Any	3%	3%	3%
Severe	<1%	<1%	<1%
Headache			
Any	15%	15%	15%
Severe	1%	1%	1%
Sweating			
Any	3%	3%	3%
Severe	<1%	<1%	<1%
Fatigue			
Any	10%	11%	10%
Severe	1%	1%	1%
Fever			
Any ($\geq 38.0^{\circ}$ C orally)	1%	1%	<1%
$\geq 40.5^{\circ}$ C	0	0	0

Source: BLA 125408/0, CSR for V58P13, Table 12.2.3-2, page 100

Myalgia, headache, and fatigue were the only solicited systemic adverse reactions reported in more than 10% of subjects in any treatment arm. The percentage of subjects with myalgia was slightly higher in the Flucelvax (12%) and Agriflu (10%) arms than the placebo arm (7%). The percentage of subjects with headache and fatigue was almost identical in the three study arms. There was no solicited systemic adverse reaction reported with more than 5% difference between any of arms.

The incidence of subjects with individual severe systemic adverse reactions was less than 1% or less in all arms for all adverse reactions.

Fever (defined as oral temperature $\geq 38.0^{\circ}$ C) was reported in 1% of subjects in both the Flucelvax and Agriflu arms and in less than 1% of subjects in the placebo arm. Severe fever, defined as oral temperature $\geq 40.5^{\circ}$ C, was not reported in the study.

The majority of solicited systemic adverse reactions were reported on Days 1 and 2; individual systemic adverse reactions in Day 7 were reported in 1% or fewer subjects.

Reviewer comment: The percentage of subjects reporting individual solicited systemic adverse reactions was similar in the three treatment arms. There was a slight increase in myalgia in the Flucelvax (12%) and Agriflu (10%) arms compared to the placebo arm

(7%). The percentage of subjects with severe reactions was low ($\leq 1\%$). The percentage of subjects with fever of 38.0°C or higher was low, and fever of 40.5°C or higher was not reported.

The applicant also collected information on the percentage of subjects who stayed home due to a solicited adverse reaction and the percentage who used analgesics or antipyretics during the seven days after vaccination. The results for these queries are shown in the table below.

Table 26: Study V58P13 - Percentage of Subjects Reporting Other Systemic Solicited Adverse Reactions in the Seven Days Post-Vaccination

	Flucelvax N=3813	Agriflu N=3669	Placebo N=3894
Stayed home due to adverse reaction	1%	2%	1%
Analgesic or antipyretic use	10%	11%	10%

Source: BLA 125408/0, CSR for V58P13, Table 12.2.3-2, page 100

Reviewer comment: The percentage of subjects who stayed home due to a solicited adverse reaction and the percentage of subjects who used analgesics or antipyretics due to a solicited adverse reaction were similar in the three treatment arms.

Unsolicited adverse events

Information on unsolicited adverse events was collected for the seven days post-vaccination; information on unsolicited AEs that necessitated physician contact was collected for Days 1-22.

Unsolicited adverse events reported in the time period Days 1-7:

The percentage of subjects reporting an adverse event (AE) in the Days 1-7 time period was 9% in the Flucelvax arm, 10% in the Agriflu arm, and 10% in the placebo arm. The organ systems for which an AE was reported are shown in the table below; only organ systems for which 2% or more of subjects reported AEs are included in the table.

Table 27: Study V58P13 - Percentage of Subjects with Unsolicited Adverse Events in Specific Organ System Classes (Organ Classes with $\geq 2\%$ of Subjects Reporting an AE)

	Flucelvax N=3813	Agriflu N=3669	Placebo N=3894
General / Injection Site	2%	3%	2%
Infections and Infestations	3%	2%	2%
Respiratory, thoracic, and mediastinal	2%	2%	2%

Source: BLA 125408/0, CSR for V58P13, Table 12.2.3-3, page 103

Reviewer comment: The percentage of subjects with unsolicited AEs in each organ system class was low. The only organ system classes for which AEs were reported in 2% or more of subjects in an arm were general / injection site, infections and infestations: and respiratory, thoracic, and mediastinal. The percentage of subjects with unsolicited AEs in individual organ system classes was similar in the three treatment arms.

Unsolicited adverse events necessitating physician contact reported in the time period Days 8-22:

The percentage reporting an AE in the Days 8-22 time period was 3% in all three study arms. The organ systems for which an AE necessitating physician contact were reported in this time

period are shown in the table below; only organ systems for which 2% or more of subjects reported AEs are included in the table.

Table 28: Study V58P13 - Percentage of Subjects with Unsolicited Adverse Events in Specific Organ System Classes (Organ Classes with $\geq 2\%$ of Subjects Reporting an AE)

	Flucelvax N=3813	Agriflu N=3669	Placebo N=3894
Infections and Infestations	1%	1%	2%

Source: BLA 125408/0, CSR for V58P13, Table 12.2.3-4, page 106

Reviewer comment: The percentage of subjects with unsolicited AEs necessitating physician contact in each organ system class was low. The only organ system classes for which AEs were reported in 2% or more of subjects in an arm were infections and infestations. The results were similar in the three treatment arms.

Unsolicited adverse events reported in the time period Days 23-181:

Only serious adverse events, new onset chronic illnesses, and AEs resulting in study withdrawal were collected during this time period. The percentage of subjects with these types of unsolicited AEs was 2% in the Flucelvax arm, 1% in the Agriflu, and 2% in the placebo arm. Adverse events were reported in fewer than 2% of subjects for each system organ class.

Reviewer comment: The percentage of subjects with unsolicited AEs in the time period from Day 23 to Day 181 was low and was similar in each study arm. The low number of subjects with AEs is due in part to the limitation in types of unsolicited AEs followed during this time period.

Reviewer analysis of unsolicited adverse events

In the Clinical Study Report, unsolicited adverse events in Study V58P13 were described by system organ class only. The adverse event (ADVERSE), concomitant medication (CMED), and comments (COMMENTS) datasets were analyzed by this reviewer for additional information on unsolicited adverse events. There were no individual unsolicited adverse events that were reported in 2% or more of subjects (>73 subjects) in a treatment arm.

Unsolicited AEs reported at least 20 times ($\geq 0.5\%$ of subjects) in any of the three treatment arms are shown in the table below

Table 29: Number of Individual Unsolicited Adverse Events Reported in > 20 Subjects in Study VP58P13

	Flucelvax N=3813	Agriflu N=3669	Placebo N=3894
Pharyngolaryngeal pain	57	62	59
Rhinitis	37	35	35
Headache	26	34	41
Upper respiratory tract infection	25	24	22
Nasopharyngitis	25	16	13
Cough	25	19	15
Injection site hemorrhage	22	31	28
Fatigue	17	28	26
Malaise	15	22	16
Diarrhea	15	16	21

Source: BLA 125408/0, CSR for V58P13, Adverse event dataset

As shown in the table above, the most commonly reported unsolicited AE in all three treatment arms was pharyngolaryngeal pain. Other upper respiratory AEs, such as rhinitis, upper respiratory tract infection, and nasopharyngitis, were also among the most frequently reported unsolicited AEs. There were more than 20 events of injection site hemorrhage reported in each of the three study arms; the preferred term was injection site hemorrhage and was further described in the datasets as injection site bruising. Although injection site ecchymosis was captured as a solicited adverse reaction, it appears that bruising lasted more seven days in a small percentage of subjects.

Unsolicited adverse events occurring in the seven days post-vaccination were analyzed in detail. As noted previously, due to the study design, all unsolicited AEs were only followed for the seven days post-vaccination. Unsolicited adverse events were reported in the first seven days post-vaccination in 350 subjects (9.1%) in Flucelvax arm (489 AEs), in 357 subjects (9.7%) in the Agriflu arm (521 AEs), and in 371 subjects (9.5%) in the placebo arm (546 AEs). The unsolicited adverse events that were reported most often in the seven days post-vaccination are shown in the table below.

Table 30: Study V58P13 - Number of Individual Unsolicited Adverse Events Reported in the Seven Days Post-Vaccination

	Flucelvax N=3813	Agriflu N=3669	Placebo N=3894
Pharyngolaryngeal pain	54	55	57
Rhinitis	33	31	33
Headache	23	30	35
Cough	23	17	15
Injection site bruising	21	31	25
Upper respiratory tract infection	20	18	13
Fatigue	17	27	22
Diarrhea	10	15	20

Source: BLA 125408/0, CSR for V58P13, Adverse event dataset

The total number of AEs and the types of individual AEs in each treatment arm were similar. The types of unsolicited AEs reported in the seven days post-vaccination were similar to those reported for the entire study period. The most commonly reported unsolicited AE in

each of the groups was pharyngolaryngeal pain. It is unclear why injection site bruising was reported commonly in the seven days post-vaccination instead of being captured as a solicited adverse event.

The datasets for individual adverse events were analyzed for any evidence of hypersensitivity, anaphylaxis, or allergic reaction. One subject in the Flucelvax arm was diagnosed with hypersensitivity after vaccination. This subject, a 26 year old white male developed mild hoarseness on the day of vaccination. He was treated with antihistamines and naproxen. This AE was judged as not vaccine related. Urticaria was reported in two subjects. One subject developed hives post-vaccination that required treatment with benadryl and steroids. Another developed hives on her ankle on the day of vaccination and hives on her forearm on day 4. She was not treated. Both AEs of urticaria were judged as vaccine-related. Another subject, a 43 year old white female, developed erythema multiforme on day 7 after vaccination with Flucelvax. Lesions appeared on her thighs, buttocks, and hands. She was treated with antihistamines, topical steroids, acyclovir, and antibiotics. This AE was also judged as not vaccine related. Seven other subjects in the Flucelvax arm reported a rash in the seven days post-vaccination. Two were moderate in intensity and the other five were mild. Five required treatment with either over-the-counter or prescription medication. Five were judged as vaccine related. Two additional subjects reported erythema on their neck and face after vaccination. One of these also complained of burning of the skin on her cheeks after vaccination; she was treated with antihistamines. Another six subjects reported pruritis without rash post-vaccination. One of the subjects with pruritis also had swelling of his eyelid.

Reviewer comment: In the opinion of this reviewer, due to the temporal relationship of these AEs with vaccination a causal association of these allergic-type reactions with Flucelvax cannot be ruled out.

In the Agriflu arm, there were no AEs of hypersensitivity or anaphylaxis. Mild urticaria was reported in a 46 year old white female beginning on the day of vaccination. The urticaria resolved within one day, and did not require treatment. Three subjects in the Agriflu arm reported a rash in the seven days post-vaccination. All three were judged to be vaccine related. Interestingly, one subject, a 40 year old female, had a rash on her face, chest, and axilla that began on day 3, lasted one day, and was accompanied by axillary tenderness, chest wall tenderness, and numbness of the elbow and arm on the right side. Two subjects reported pruritis without rash.

In the placebo arm, there were no AEs with the preferred term of hypersensitivity or anaphylaxis. However, urticaria was reported in two subjects. A 41 year old female developed hives at the injection site and on her shoulder and back after vaccination. Her urticaria was determined to be mild in intensity and was not treated. The other subject, a 38 year old white male, reported urticaria on his face on day 3 and did not receive treatment. Two subjects in the placebo arm had rashes in the first week after vaccination. Both rashes were reported on the day of vaccination; neither required treatment.

Reviewer comment: As described above, AEs consistent with allergy to the vaccine were uncommon but were reported slightly more often after vaccination with Flucelvax (N=19) compared to Agriflu (N=6) or placebo (N=4). Although the case of erythema multiforme after Flucelvax is concerning, it was a single case and no similar AEs were reported.

The number of unsolicited AEs in the first seven days post-vaccination treated with prescription medication was 82 in the Flucelvax arm, 81 in the Agriflu arm, and 79 in the placebo arm. The individual types of unsolicited AEs treated with prescription medications varied. Over-the-counter medications were recommended to treat 140 in the Flucelvax arm, 151 AEs in the Agriflu arm, and 172 in the placebo arm. The types of AEs treated with over-the-counter medications were similar to the most common unsolicited AEs in the seven days post-vaccination and were similar between the treatment arms.

Of note, there were no cases of Guillain Barré syndrome, and no subject had signs and / or symptoms consistent with oculorespiratory syndrome.

Reviewer comment: The number of subjects with unsolicited AEs and the types of unsolicited AEs reported in the seven days post-vaccination were similar between the three treatment arms. In addition, the types of unsolicited AEs were consistent with infections and other common illnesses observed in adults. Overall, no safety signals were identified by this reviewer.

Study discontinuations due to adverse events

Adverse events leading to premature study discontinuation were reported in less than 1% of subjects in each arm. None of the AEs were judged by study investigators to be related to study vaccination. Three subjects in the Flucelvax arm discontinued prematurely due to an AE; one discontinued on Day 153 due to death from respiratory arrest associated with obesity, one on Day 75 due to death from unknown cause, and one on Day 99 due to skull fracture, extradural hematoma, and subdural hematoma. One subject in the Agriflu arm discontinued prematurely due to death from homicide. One subject in the placebo arm discontinued the study prematurely due to an AE; this subject died on Day 33 due to a spontaneous cerebral hemorrhage. Study deaths are described in the next section of this review.

6.1.11.3 Deaths

There were four deaths in the study: two in the Flucelvax arm, one in the Agriflu arm, and one in the placebo arm. None of the deaths were judged by the investigators as related to study vaccination. The deaths are described below.

Subject 09/281 was a 35 year old Black female with a history of obesity and hypertension who received Flucelvax in Study V58P13. She developed trouble breathing approximately five months post-vaccination and was admitted to the hospital. During the hospitalization, she suffered respiratory arrest, and resuscitation efforts failed. She died on Day 153; death was attributed to obesity (weight of approximately 400 lbs).

Subject 35/169, a 38 year old Caucasian male, was vaccinated with Flucelvax. He had a history of hypertension, depression, and alcoholism; he also had a history of hypoglycemia, hypokalemia, and hyponatremia with no known etiology. His concomitant medications were bisoprolol fumarate, candesartan cilexetil, and ramipril. He was found unconscious on Day 12 and was hospitalized; the loss of consciousness was attributed to diarrhea and vomiting, and he was discharged the following day. He was found dead on Day 75; the death was presumed to be due to his one of his medical conditions. No autopsy report is available for this subject.

Subject 17/299 was a 37 year old Hispanic male who was vaccinated with Agriflu. He died on Day 99 as result of a homicide (stabbing).

Subject 31/320, who was vaccinated with placebo, was a 31 year old Caucasian male. He experienced a massive cerebral hemorrhage on Day 26 due to an arteriovenous malformation. He never regained consciousness, and he died seven days later when all active treatment was stopped.

Reviewer comment: In the opinion of this reviewer, none of these deaths appear to have been related to the study vaccine.

6.1.11.4 Nonfatal Serious Adverse Events and New Onset Chronic Illnesses

Serious adverse events were reported in 1% of subjects in each of the three study arms: 42 subjects in the Flucelvax arm, 35 in the Agriflu arm, and 38 in the placebo arm. Of these SAEs, nine in the Flucelvax arm, two subjects in the Agriflu arm, and two in the placebo arm experienced SAEs in the 21 days post-vaccination. None of the SAEs were considered by the investigators to be vaccine related. Serious adverse events that were reported in at least two subjects in any of the subject arms are shown in the following table.

Table 31: Study V58P13 - Number of Subjects with Serious Adverse Events (≥ 2 Subjects in Any Arm) During Entire Study Period

	Flucelvax N=3813	Agriflu N=3669	Placebo N=3894
Ankle fracture	2	0	1
Intervertebral disc protrusion	2	0	2
Appendicitis	1	1	3
Nasal septum deviation	1	2	0
Pneumonia	0	1	2
Hemorrhagic ovarian cyst	0	2	0
Back pain	0	0	2
Pharyngitis	0	0	2

Source: BLA 125408/0, CSR, Table 14.3.1.1.7, pages 544-550

Reviewer comment: There was no increase in the overall incidence of serious AEs or in any type or class of serious AEs in either the Flucelvax or Agriflu arm compared to the placebo arm. In the opinion of this reviewer, none of these serious AEs were likely to be related to the study vaccines.

On analysis of the serious adverse events during the first seven days post-vaccination, serious AEs were reported in five subjects. None of these SAEs was judged to be vaccine related.

Less than 1% of subjects in each study arm experienced a new chronic illness. There were five subjects in the Flucelvax arm with a new chronic illness (two with hypertension and one each with depression, gastroesophageal reflux, and psoriasis), two in the Agriflu arm (hypertension and ankylosing spondylitis), and six in the placebo arm (two with hypertension and one each with asthma, emphysema, hypercholesterolemia, and hypothyroidism).

Reviewer comment: No overall increase of new onset chronic diseases and no increase in any individual type or class of new onset chronic diseases was observed in the two

treatment arms compared to the placebo arm. The types of chronic diseases were consistent with conditions commonly observed in adult populations.

6.1.12 Comments & Conclusions

The results of Study V58P13 provide the primary basis for demonstration of the efficacy and safety of Flucelvax in adults. In this large, randomized, placebo-controlled trial in healthy adults 18-49 years of age, vaccine efficacy for CDC-ILI influenza disease caused by influenza strains matched to the vaccine was 83.8% (LB 95% CI: 60%), clearly demonstrating the effectiveness of Flucelvax. In secondary analyses, vaccine efficacy for mis-matched strains was 58.7% (LB 95% CI: 55%). The most commonly observed adverse events following vaccination with Flucelvax were local injection site reactions, particularly pain and erythema, headache, malaise, and fatigue. Unsolicited and serious adverse events were uncommon. The numbers and types of unsolicited and serious AEs were similar in the three treatment arms. There were a small number of subjects with AEs consistent with an allergic reaction to Flucelvax, but the number of subjects was very small, the types of reactions were varied, and none of the AEs were serious.

6.2 Trials #2 Study V58P4 (NCT Number 00492063)

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

6.2.1 Objectives

The primary objective for this study was to evaluate immunogenicity of a single 0.5 mL intramuscular injection of Flucelvax and an egg-derived influenza vaccine (Agriflu) in compliance with the requirements of the European Medicines Agency (EMA) recommendations.

The secondary objectives were to:

- Demonstrate non-inferiority of Flucelvax to Agriflu using seroconversion rate, sufficient increase in GMT, and percentage of subjects with post-vaccination HAI titer of 1:40 or higher after a single dose of study vaccine and
- Evaluate safety and tolerability of a single dose of Flucelvax and Agriflu.

Reviewer comment: Although this study evaluated both Flucelvax and Agriflu, this review focuses on the objectives relating to Flucelvax.

This study was not conducted under US IND and the endpoints, which will be discussed later in this review, were designed to meet European Medicines Agency criteria for demonstration of immunogenicity.

6.2.2 Design Overview

Study V58P4 was a Phase 3, observer-blind, active-controlled, multi-center, non-inferiority immunogenicity study of Flucelvax and Agriflu in healthy adults 18 years of age and older. Enrollment of subjects was stratified by age (18-60 years and ≥ 61 years) and then randomized in a 1:1 ratio to either Flucelvax or Agriflu.

Reviewer comment: In studies of influenza, elderly is defined as 61 years of age and older by the EMA and as 65 years of age and older by the FDA (See CPMP/BWP/214/96

and FDA Guidance for Industry, “Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines”). This study was conducted using EMA standards, including the definition of elderly. However, the study was not conducted under US IND and was initiated prior to publication of the FDA Guidance. CBER agreed with the applicant that the results of this study could be reanalyzed using the US definition of elderly (18-64 years and ≥ 65 years) in order to support the safety and immunogenicity of the elderly for US licensure. In addition, CBER also requested additional analyses of the immunogenicity results for subjects from 50 through 64 years of age to support efficacy in this age group, since the clinical endpoint included subjects from 18 through 49 years of age. The results for these age groups are included as post-hoc immunogenicity analyses in this review. The results are also discussed in Sections 7.1.11 and 8 of this review.

Subjects received a single, 0.5mL dose of study vaccine in the deltoid muscle. Subjects were instructed not to take antipyretic medication for prevention of fever prior to vaccination.

Subjects were monitored at the study site for 30 minutes post-vaccination. During that time they were provided with diary cards to collect information on adverse reactions to study vaccine. (See safety monitoring section of this review). Subjects were followed for six months post-vaccination.

Serum samples were collected pre-vaccination and on Day 22 for determination of antibody response to study vaccine.

6.2.3 Population

Study subjects were healthy adult volunteers 18 years of age and older.

Subjects were excluded from study participation for any of the following:

- laboratory-confirmed influenza disease within the previous 6 months,
- receipt of an influenza vaccine within 6 months or plans to receive influenza vaccine within three weeks of study vaccination,
- history of hypersensitivity to any component of the study vaccine or of chemically related substances such as allergy to eggs or egg products,
- acute infectious or respiratory disease within three days of enrollment,
- any serious disease such as cancer, autoimmune disease, impaired immune function, advanced arteriosclerotic disease, complicated diabetes mellitus, COPD requiring oxygen therapy, CHF, hepatic disease, or renal disease,
- any condition that may have interfered with evaluation of the study objectives or the safety of the subject,
- receipt of another vaccine or investigational agent within 60 days or planned receipt within three weeks of study vaccination,
- bleeding diathesis or
- history of drug or alcohol abuse

6.2.4 Study Treatments or Agents Mandated by the Protocol

Study subjects received a single, 0.5 mL dose of study vaccine intramuscularly in the deltoid muscle of the non-dominant arm; study vaccines were Flucelvax (cell-derived vaccine) and

Agriflu (egg-derived vaccine). Flucelvax and Agriflu contained 15 µg of HA for each of the following strains that were recommended for the 2004-2005 influenza season in the Northern Hemisphere:

- A/New Caledonia/20/99 (H1N1-like),
- A/Fujian/411/2002 (H3N2-like), and
- B/Shanghai/361/2002 (B-like).

6.2.5 Sites and Centers

Study V58P4 was conducted at 5 study sites in Poland. The study was not conducted under US IND.

6.2.6 Surveillance/Monitoring

Subjects were seen at the study center on Days 1, 22, and 180. The study window for the Day 22 visit was originally Days 21-25, but was widened to Days 20-33 after data were unblinded.

Reviewer comment: The visit window for the Day 22 visit was widened post-hoc so that 25 subjects who were seen outside of the original study window could be included in the Per Protocol population. Since antibody levels to influenza virus are thought to peak around three to four weeks post-vaccination in people previously exposed to influenza viruses or vaccines, widening the window might have resulted in capturing some antibody titers that were either still rising or beginning to decline in these subjects, but should not have introduced bias resulting in higher influenza antibody titers.

A medical history and physical examination were performed on all subjects on Day 1, prior to vaccination. Physical examinations were repeated as needed at the Day 22 visit.

Subjects received a single, 0.5 mL dose of study vaccine in the deltoid muscle on Day 1 and remained in clinic for 30 minutes after vaccination to monitor for any immediate reactions. Subjects were discharged with a Diary Card and instructed to record all AEs and solicited adverse reactions for the six days post-vaccination as well as information on all unsolicited AEs from Days 7 to 22. Diary Cards were collected at the Day 22 visit. Information on serious AEs, AEs that resulted study withdrawal, and pregnancies was collected for the 180 days post-vaccination.

Local solicited adverse events monitored were ecchymosis, erythema, induration, swelling, and pain at the injection site. Systemic solicited adverse reactions monitored were chills, malaise, arthralgia, headache, sweating, fatigue, and fever. Subjects were instructed to measure their temperature by the axillary route and record the result daily. Fever was defined as axillary temperature $\geq 38.0^{\circ}\text{C}$. Mild fever was defined as 38.0 to 38.9°C , and moderate fever was defined as 39.0 to 39.9°C . Subjects were also to record use of any analgesics or antipyretics for solicited adverse reactions. Solicited adverse reactions also included a query on whether subject stayed at home due to the adverse reaction.

Reviewer comment: With the exception of mild and moderate fever, the grading scale for severity of solicited adverse reactions was not provided in the Clinical Study Report. Since the study was not reviewed under US IND, it is unclear how the grading scales were defined.

6.2.7 Endpoints and Criteria for Study Success

The primary endpoint was the antibody response after a single dose of study vaccine for each vaccine influenza strain. Antibody titers were measured pre-vaccination and on Day 22 post-vaccination. The antibody response was then analyzed using seroconversion rates, the percentage of subjects with HAI titer $\geq 1:40$, and geometric mean titers.

Antibody response assays were performed at the Chiron Behring Technical Development department in Marburg, Germany. The initial HAI tests were performed using both cell- and egg-derived antigens. Since there were problems with pipette calibration at the site performing the assays, all assays were repeated and due to limitations in the amount of sera available for retesting, only assays using egg-derived antigens were provided in this BLA.

Reviewer comment: Please see the Chemistry reviews and Section 4.2 of this review for a discussion of the pipetting calibration problems that occurred with assays conducted for this study as well as several other studies submitted in this BLA. If the pipetting issues affected results, it would have been to lower antibody titers; therefore, it is unlikely that the study results were biased toward over-estimation of titers by the pipetting errors.

Results were provided using egg-derived antigens in the assays for antibody response. Choice of egg-derived antigens or cell-derived antigens in the HAI assay could potentially impact results, and which assay is likely to provide the most meaningful results for a cell-derived vaccine is not known. Since the egg-derived antigens were used in this study, any negative effect of using a “mis-matched” antigen would likely have resulted in lower Flucelvax titers relative to the egg-derived vaccine control. Therefore, any bias is more likely to have favored the control vaccine in the comparative analysis.

6.2.8 Statistical Considerations & Statistical Analysis Plan

Subjects were stratified by age (18-60 years and ≥ 61 years) and then randomized in a 1:1 ratio to either Flucelvax or Agriflu. Two randomization lists were prepared by Chiron (now Novartis) Biostatistics and Clinical Data Management Department. The study was observer-blind. Designated study personnel who administered the study vaccine had no further contact with the study subject, and study personnel monitoring outcomes were blinded to treatment assignment.

The primary endpoint was the antibody response after a single dose of study vaccine for each vaccine influenza strain. Antibody titers were measured pre-vaccination and on Day 22 post-vaccination. Three different assessments of immunogenicity were calculated from the antibody titers: the seroconversion rate at Day 22, the percentage of subjects with HAI titer $\geq 1:40$ at Day 1 and at Day 22, the geometric mean titers at Day 1 and at Day 22, and the Day 22/Day 1 geometric mean ratio. Demonstration of immunogenicity was assessed according to the requirements of the EMA (CPMP/BWP/214/96) and differed by age of subject. Immunogenicity would be demonstrated for subjects from 18 to 60 years of age if the point estimate for the results of at least one of the three parameters met the following requirements:

The seroconversion rate was $>40\%$

The proportion of subjects with a post-vaccination HAI titer $\geq 1:40$ was $> 70\%$, or

The mean geometric increase was > 2.5 .

Immunogenicity would be demonstrated for subjects 61 years of age and older if the point estimate for the results of at least one of the parameters met the following requirements:

The seroconversion rate was $>30\%$

The proportion of subjects with a post-vaccination HAI titer $\geq 1:40$ was $> 60\%$, or

The mean geometric increase was > 2.0 .

Reviewer comment: The criteria used by the EMA for demonstration of immunogenicity are less stringent than the criteria described in the FDA Guidance for Industry “Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines.” Although the same thresholds for demonstration of immunogenicity are used by EMA and FDA, in the FDA Guidance: the *lower bound of the 95% confidence interval* for parameter instead of the point estimate must meet the immunogenicity threshold, and the criteria must be met for both seroconversion rate and for the percentage of subjects with post-vaccination HAI titers of 1:40 or greater.

It must be noted that the EMA criteria are used for yearly registrational studies of licensed influenza vaccines and the FDA criteria were developed for the licensure of trivalent influenza vaccines using the accelerated approval mechanism. Although these are important immunogenicity benchmarks, and they are analyzed below, they are not the criteria by which Flucelvax is being evaluated for licensure for use in people 50 years of age and older. For individuals aged 18 to 49 years, a clinical endpoint study is the primary basis of efficacy. For individuals 50 years of age and older, effectiveness is inferred by demonstration of clinical efficacy in the younger age group together with demonstration of non-inferiority on immunogenicity endpoints compared with a US-licensed influenza vaccine. Together, favorable outcomes on these analyses can provide adequate rationale to support approval for use in the older age groups.

The criteria for demonstrating that Flucelvax was non-inferior to Agriflu were:

- The lower bound 95% confidence interval for the difference in seroconversion rate in the Flucelvax arm minus the seroconversion rate in the Agriflu arm was $> -10\%$ for all three influenza antigens, and
- The lower bound 95% confidence interval for the ratio of GMRs (Flucelvax/Agriflu) at Day 22 was > 0.5 for all three influenza antigens.

The populations analyzed included:

- All randomized population defined as all subjects enrolled, randomized, and included in the demographic dataset,
- Intention-to-treat (ITT) population, Immunogenicity defined as all subjects in the randomized population who received the study vaccine and provided one evaluable serum sample before and after baseline,
- Per protocol (PP) population defined as subjects in the intention-to-treat population who received the vaccine correctly, provided evaluable data before and after vaccination, and had no major protocol violation prior to unblinding (a major protocol violation is one that is considered to have an impact on results), and
- Safety population defined as all subjects who were vaccinated and who provide post-vaccination safety data.

The Per Protocol population was considered the primary immunogenic population.

6.2.9 Results

6.2.9.1 Study Population and Disposition

Study V58P4 was conducted at 5 study sites in Poland (four sites in Krakow and one in Kielce). The first study subject was enrolled on September 14, 2004, and the last subject completed the study on May 16, 2005.

6.2.9.2 Populations Enrolled/Analyzed and Subject Disposition

A total of 2,654 subjects were enrolled, randomized, and vaccinated: 1330 in the Flucelvax arm and 1324 in the Agriflu arm. Of these, 1300 were in the 18 to 60 year age group and 1354 were in the 61 years of age and older subgroup. See the following table for a summary of study subject disposition.

Table 32: Study V58P4 - Subject Disposition

	18-60 Years		≥ 61 Years	
	Flucelvax	Agriflu	Flucelvax	Agriflu
Enrolled and Vaccinated	652	648	678	676
Completed study	642	634	667	666
Premature discontinuations	10 (1.5%)	14 (2.2%)	11 (1.6%)	10 (1.5%)
Death	0	0	1	2
Adverse event	0	0	0	0
Consent withdrawn	4	3	5	4
Lost to follow-up	6	11	5	3
Protocol deviation/violation	0	0	0	1

Source: BLA 125408/0, CSR for V58P4, Flowchart page 71 and Table 14.1.1.2, page 150-152

More than 97% of subjects in each study arm completed the study. Most of the premature study discontinuations occurred between the Day 22 and Day 180 visit (19 in the 18-60 year subgroup and 17 in the ≥ 61 year subgroup). The majority of premature study discontinuations in each study arm were due to loss to follow-up and withdrawal of consent. There were three premature discontinuations due to death; see Section 6.2.12.3 for a discussion of these three subjects.

Reviewer comment: The percentage of subjects with premature discontinuation was relatively small and was similar between the Flucelvax arm and the Agriflu arm and between the younger and older age subgroups. In addition, the majority of premature discontinuations occurred after Day 22; and therefore, did not affect the immunogenicity outcome. It appears that study follow-up procedures were appropriate and subject retention rates should not have negatively impacted the study outcome.

6.2.9.3 Protocol deviations

In the 18 to 60 year age subgroup, protocol violations were reported in 16 (2.4%) subjects in the Flucelvax arm and in 24 (3.7%) in the Agriflu arm. The protocol deviations were loss to follow-up (N=17), post-vaccination blood draw outside the study window (N=14), consent withdrawn (N=7), and pregnancy (N=3). Major protocol deviations resulting in exclusion from the Per Protocol population were reported for six subjects: in the Flucelvax arm, one subject had their

blood drawn outside the study window and one withdrew consent, in the Agriflu arm, four subjects withdrew consent.

In the 61 years of age and older age cohort, protocol violations were reported in 22 (3.2%) subjects in the Flucelvax arm and in 15 (2.2%) in the Agriflu arm. The protocol deviations were post-vaccination blood draw outside the study window (N=15), consent withdrawn (N=9), loss to follow-up (N=8), death (N=3), receipt of an excluded medication (N=1), and failed to meet exclusion criteria (N=1). Major protocol deviations resulting in exclusion from the Per Protocol population were reported for eight subjects: in the Flucelvax arm, three subjects had their blood drawn outside the study window, one met exclusion criteria because of hepatic cirrhosis, and one withdrew consent, in the Agriflu arm, two subjects withdrew consent.

Reviewer comment: The percentage of subjects with protocol violations and the number of subjects with major protocol violations were low and were unlikely to have affected the study results substantially. The study windows for the Day 22 visit and blood draw were changed post-hoc to allow for fewer major protocol violations and resulted in 25 more subjects being included in the Per Protocol population. It is possible that antibody titers obtained at later periods after Day 22 were lower than those obtained around Day 22. Therefore, it is unlikely that resulting antibody titers would bias the results in favor of Flucelvax. In addition, the number of subjects was small, and therefore, this post-hoc change in the study window was unlikely to have had a substantial effect on the study results.

Nine subjects (<1%) were excluded from the Intent-to-Treat study population -- three subjects in the Flucelvax arm and six in the control arm. An additional five subjects, all in the Flucelvax arm were excluded from the Per Protocol population.

Reviewer comment: The differences between the vaccinated population, the ITT population, and the PP population were small. Therefore, the PP populations were appropriate populations for analysis of immunogenicity.

6.2.9.4 Demographics

The majority of study subjects were female (54%); all were Caucasian; and 49.7% had previously been vaccinated against influenza. Demographic and baseline characteristics of each study arm are shown in the table below.

Table 33: Study V58P4 - Demographic and Baseline Characteristics for Randomized Population

	18-60 Years		≥ 61 Years	
	Flucelvax N=652	Agriflu N=648	Flucelvax N=678	Agriflu N=676
Mean Age (Years)	38.7	38.3	69.1	68.8
Gender				
Female	376 (58%)	371 (57%)	389 (57%)	375 (55%)
Race				
Caucasian	652 (100%)	648 (100%)	678 (100%)	676 (100%)
Vaccinated in Previous Year	645 (48%)	675 (51%)	399 (59%)	402 (59%)

Source: BLA 125408/0, CSR for V58P4, Table 14.1.1.3, page 164-169

Reviewer comment: As shown in the table above, the demographics and baseline characteristics, with exception of mean age, were similar in the four study groups. All subjects were Caucasian, which is not representative of the racial/ethnic composition of the US population. However, there is no known difference in HAI antibody response to other influenza vaccines by race and ethnicity.

6.2.9.5 Immunogenicity Analyses

6.2.9.5.1 Analyses of Primary Endpoint(s)

The primary objective was to evaluate the immunogenicity of Flucelvax compared to Agriflu according to the requirements of the EMA/CHMP recommendations. According to EMA/CHMP recommendations, immunogenicity is demonstrated if one of the following is met:

- Point estimate for HAI seroconversion rate $\geq 40\%$ and for elderly $\geq 30\%$,
- Point estimate for percentage of subjects with post-vaccination HAI titer $\geq 1:40$ of $\geq 70\%$ for adults and $\geq 60\%$ for elderly, and
- Point estimate for GMR for adults ≥ 2.5 and for elderly ≥ 2.0 .

Seroconversion was defined as negative pre-vaccination serum and post-vaccination HAI titer $\geq 1:40$ or at least a four-fold increase in HAI titers. Geometric mean ratio was defined as the Day 22 to Day 1 ratio between geometric mean HAI titers.

Immunogenicity results for the 18 to 60 year age group are shown in the following table.

Table 34: Study V58P4 - Results (Point Estimates) for Seroconversion Rate, Percentage of Subjects with HAI Titers $\geq 1:40$, and Geometric Mean Ratio in Subjects 18 to 60 Years of Age (Per Protocol Population)

	Flucelvax N=650			Agriflu N=644		
	H3N2	H1N1	B	H3N2	H1N1	B
SCR	63%	69%	85%	64%	67%	81%
% $\geq 1:40$ Baseline	65%	29%	16%	63%	33%	18%
% $\geq 1:40$ Day 22	99%	92%	90%	99%	92%	91%
GMR	5.99	11	13	7.08	11	12

Source: BLA 125408/0, CSR for V58P4, Tables 11.4.1.1.1-1 to 11.4.1.1.1-3, pages 80-82

The EMA / CHMP criteria for demonstration of immunogenicity were met for both Flucelvax and for Agriflu.

Immunogenicity results for the 61 years and older age group are shown in the following table.

Table 35: Study V58P4 - Results (Point Estimates) for Seroconversion Rate, Percentage of Subjects with HAI Titers $\geq 1:40$, and Geometric Mean Ratio in Subjects ≥ 61 Years of Age (Per Protocol Population)

	Flucelvax N=672			Agriflu N=674		
	H3N2	H1N1	B	H3N2	H1N1	B
SCR	68%	55%	80%	65%	55%	73%
% $\geq 1:40$ Baseline	66%	30%	23%	59%	31%	20%
% $\geq 1:40$ Day 22	97%	85%	90%	98%	85%	89%
GMR	7.25	5.74	12	8.36	5.96	9.25

Source: BLA 125408/0, CSR for V58P4, Tables 11.4.1.1.1-1 to 11.4.1.1.1-3, pages 80-82

The EMA / CHMP criteria for demonstration of immunogenicity were also met in the 61 years of age and older subgroup. Therefore, the protocol-specific primary endpoint of the study was met.

6.2.9.5.2 Analyses of Secondary Endpoints

Immunologic non-inferiority of Flucelvax to Agriflu was evaluated as a secondary analysis.

The criteria for demonstration of non-inferiority were:

The lower bound of the 95% CI for the difference in HAI seroconversion rates was $> -10\%$

The lower bound of the 95% CI for the difference in the percentage of subjects with post-vaccination HAI titers $\geq 1:40$ was $> -10\%$ and

The lower bound of the 95% CI for the HAI GMT ratio (Flucelvax GMT / Agriflu GMT) was > 0.5 .

These criteria needed to be met for each influenza strain in the vaccine. Results for the non-inferiority comparison are shown in the following tables.

Table 36: Study V58P4 - Point Estimates (Lower Bound 95% Confidence Intervals) for Non-Inferiority Comparisons of Flucelvax to Agriflu

	Differences in Flucelvax and Agriflu Arms		
	Seroconversion Rate Difference Flucelvax-Agriflu (95% CI)	Difference in Percentage with HAI Titer \geq 1:40 Flucelvax-Agriflu (95% CI)	GMT Ratio Flucelvax/Agriflu (95% CI)
Subjects 18-60 Years of Age			
H3N2	-1% (-6%)	0 (-1%)	0.85 (0.72)
H1N1	2% (-3%)	0 (-3%)	1.07 (0.9)
B	4% (0)	0 (-3%)	1.14 (0.99)
Subjects \geq 61 Years of Age			
H3N2	3% (-2%)	-1% (-2%)	0.87 (0.74)
H1N1	0 (-6%)	-1% (-4%)	0.96 (0.82)
B	6% (2%)	1% (-2%)	1.27 (1.11)

Source: BLA 125408/0, CSR for V58P4, Tables 11.4.1.2.1-1 and 11.4.1.2.2-1, pages 87-88

As shown in the previous table, non-inferiority of Flucelvax to Agriflu was demonstrated in both age subgroups and for all three influenza strains.

Reviewer comment: Although non-inferiority analyses were secondary endpoints, these analyses provided the basis to infer Flucelvax effectiveness in subjects 50 years and older. Non-inferiority was demonstrated in the age subgroups for subjects 50 through 64 years and \geq 65 years and these results are shown in the summary of efficacy in this review.

6.2.9.5.3 Subpopulation Analyses

Subgroup analyses were provided by previous vaccination and gender. The results for subjects with baseline HAI titers less than 1:40 are shown in the tables below.

Table 37: Study V58P4 - Results (Point Estimates) for Seroconversion Rate, Percentage of Subjects with HAI Titers $\geq 1:40$, and Geometric Mean Ratio in Subjects 18 to 60 Years of Age With HAI Titers $< 1:40$ at Baseline (Per Protocol Population)

	Flucelvax			Agriflu		
	H3N2 N=226	H1N1 N=459	B N=549	H3N2 N=236	H1N1 N=434	B N=526
SCR	94%	83%	88%	93%	83%	87%
% $\geq 1:40$ Day 22	97%	88%	89%	97%	88%	89%
GMR	17	20	16	27	20	15

Source: BLA 125408/0, CSR for V58P4, Tables 11.4.1.3.1-1 to 11.4.1.3.1-3, pages 90-92

Reviewer comment: The number of subjects studied varied by influenza strain. For example, 226 subjects were included for response to H3N2 in the Flucelvax arm compared to 549 included for the response to influenza B. The reason for this inconsistency is unclear. If sera from all subjects were not available for all analyses, the affects of randomization would be lost. In addition, the loss of almost half the number of subjects in some test groups may have affected the results for that group.

The EMA / CPMP criteria for demonstration of immunogenicity were met for this subgroup of adult subjects who were had HAI titers less than 1:40 at baseline.

Table 38: Study V58P4 - Results (Point Estimates) for Seroconversion Rate, Percentage of Subjects with HAI Titers $\geq 1:40$, and Geometric Mean Ratio in Subjects ≥ 61 Years of Age With HAI Titers $< 1:40$ at Baseline (Per Protocol Population)

	Flucelvax			Agriflu		
	H3N2	H1N1	B	H3N2	H1N1	B
SCR	90%	69%	86%	91%	72%	81%
% $\geq 1:40$ Day 22	92%	78%	87%	95%	79%	87%
GMR	22	8.93	16	29	10	12

Source: BLA 125408/0, CSR for V58P4, Tables 11.4.1.3.2-1 to 11.4.1.3.2-3, pages 93-95

The EMA / CPMP criteria for demonstration of immunogenicity were also met in elderly subjects with HAI titers less than 1:40 at baseline.

Reviewer comment: The point estimates for seroconversion rate, percentage of subjects with post-vaccination HAI titers $\geq 1:40$, and GMR were similar in the Flucelvax and Agriflu arms and in both age groups for subjects who had baseline HAI titers $< 1:40$.

Subgroup analyses were also performed for gender. The results for both age subgroups combined are shown in the following table.

Table 39: Study V58P4 - Immunogenicity Results by Gender for the Combined Age Subgroups

	Flucelvax Arm			Agriflu Arm		
	SCR	% HAI Titer ≥ 1:40	GMR	SCR	% HAI Titer ≥ 1:40	GMR
Females						
H3N2	71%	98%	7.52	67%	99%	8.45
H1N1	66%	89%	9.16	65%	90%	8.88
B	84%	90%	14	80%	90%	12
Males						
H3N2	58%	98%	5.52	61%	98%	6.85
H1N1	57%	87%	6.72	57%	86%	6.79
B	80%	91%	11	73%	89%	9.23

Source: BLA 125408/0, CSR for V58P4, Tables 14.2.1.1.5, 14.2.1.1.5, and 14.2.1.3.5, pages 355-372, 454-471, and 553-570

Reviewer comment: Seroconversion rates and geometric mean ratios for each influenza antigen were higher in females than males. The percentages of subjects with HAI titers of 1:40 or greater were similar for females and males. The results were similar in the Flucelvax and Agriflu arms. On further analysis, the GMTs were similar for each gender at baseline, as shown for subjects in the Flucelvax arm in the table below.

Table 40: Geometric Mean Titers at Baseline by Gender for Subjects in the Flucelvax Arm

	Females	Males
H3N2	42	53
H1N1	15	18
B	11	13

Source: BLA 125408/0, CSR for V58P4, Table 14.2.1.3.5, pages 553-570

As shown in this table, differences in seroconversion rate and GMR do not appear to be related to baseline antibody titers. Differences in males and females were observed in both age subgroups. It must be noted that antibody response to influenza vaccines have not been shown to vary by gender, that the study was not designed or powered to identify differences by gender, that the results were similar in both the Flucelvax and Agriflu arms, that the EMA criteria for demonstration of immunogenicity were met for both males and females, and that clinical efficacy estimate was slightly higher for males than females in Study V59P13.

Since only Caucasians were enrolled in this study and because the study was conducted in a single country, there are no subgroup analyses by race or by country / region.

6.2.9.5.4 Additional Immunogenicity Analyses Requested by CBER

CBER requested analyses of the immunogenicity results by age cohorts 18 through 49 years, 50 through 64 years, and 65 years and older. The results for the age groups 18 through 49 and 50 through 64 years are shown in the following table.

Table 41: Study V58P4 – Results (Point Estimates and 95% CIs) for Percentage of Subjects with Post-Vaccination HAI Titers $\geq 1:40$, and Seroconversion Rate in Subjects 18 through 49 and 50 through 64 Years of Age)

Vaccine strain	18 through 49 Years		50 through 64 Years	
	% HI Titer $\geq 1:40$	% Seroconversion	% HI Titer $\geq 1:40$	% Seroconversion
	(95% CI %)	(95% CI %)	(95% CI %)	(95% CI %)
A/H1N1	94	73	84	57
	(91-96)	(69-77)	(79-88)	(52-63)
A/H3N2	99	63	99	66
	(98-100)	(59-68)	(97-100)	(61-71)
B	93	88	87	77
	(90-95)	(84-90)	(83-90)	(70-79)

Source: Applicant communication to CBER, October 17, 2012

Reviewer comment: Since the clinical endpoint study enrolled subjects 18 through 49 years of age, this analysis was requested to examine immunogenicity in subjects 50 through 64 years of age.

Non-inferiority analyses for comparison of these age groups to a US-licensed comparator were also requested and are shown in the following table.

Table 42: Study V58P4 - Non-inferiority Analysis of Flucelvax to Agriflu in Adults 18 through 49 Years and 50 through 64 Years of Age

	Vaccine Group Ratio/Difference		
	(95% CI)		
	Flucelvax Versus Agriflu		
	A/H1N1	A/H3N2	B
Subjects 18 through 49 years			
GMTs ratio	0.96	0.98	1.07
(Flucelvax / Agriflu)	(0.81, 1.13)	(0.87, 1.11)	(0.93, 1.23)
Difference in Seroconversion Rates	2%	2%	5%
(Flucelvax – Agriflu)	(-4, 8)	(-5, 8)	(1, 10)
Subjects 50 through 64 Years			
GMTs ratio	0.96	0.87	1.23
(Flucelvax / Agriflu)	(0.79, 1.16)	(0.74, 1.02)	(1.02, 1.48)
Difference in Seroconversion Rates	1%	-2%	3%
(Flucelvax – Agriflu)	(-6, 8)	(-9, 5)	(-4, 9)

Source: Applicant communication to CBER, October 17, 2012

Reviewer comment: The protocol-defined criteria for demonstration of non-inferiority of Flucelvax to Agriflu were met in both age groups. These results allow extrapolation of clinical effectiveness of Flucelvax in 18 through 49 year olds, demonstrated in Study V58P13, to the age group 50 through 64 years of age.

In the original study, elderly was defined as 61 years of age and older. However, elderly is defined by FDA as 65 years of age and older. Therefore, immunogenicity analyses were also requested for the subjects 65 years of age and older. Results for this age group are shown in the following two tables.

Table 43: Study V58P4 - Percentage (%) of subjects with Post-Vaccination HI Titers \geq 1:40 and Seroconversion Rate in Flucelvax Recipients 65 Years of Age and Older

<u>Vaccine strain</u>	<u>% of Subjects with HI Titer \geq1:40 (95% CI %)</u>	<u>% of Subjects with Seroconversion (95% CI %)</u>
<u>A/H1N1</u>	<u>86</u> (83-89)	<u>55</u> (50-59)
<u>A/H3N2</u>	<u>97</u> (95-98)	<u>68</u> (64-72)
<u>B</u>	<u>90</u> (87-93)	<u>80</u> (76-84)

Source: BLA 125408/0, Section 1.14.1.2

Table 44: Study V58P4 - Non-inferiority Analysis of FLUCELVAX to a US licensed Comparator (Agriflu) in Adults 65 Years of Age and Older (Study 2*)

	Vaccine Group Ratio/Difference (95% CI) Flucelvax Versus Agriflu		
	A/H1N1	A/H3N2	B
GMTs ratio (Flucelvax / Agriflu)	1.06 (0.92, 1.22)	0.97 (0.84, 1.12)	1.28 (1.1, 1.48)
Difference in Seroconversion Rates (Flucevax – Agriflu)	-1% (-7, 6)	3% (-2, 9)	7% (1, 12)

Source: BLA 125408/0, Section 1.14.1.2

Reviewer comment: The HAI antibody response to Flucelvax was non-inferior to the response to Agriflu. Therefore, the clinical efficacy results in younger adults may be extrapolated to the elderly age group.

6.2.9.6 Safety Analyses

All of the study subjects were vaccinated and all are included in at least one of the safety analysis.

6.2.9.6.1 Non-Serious Adverse Events

Solicited adverse reactions

Solicited adverse reactions were recorded for the seven days after vaccination. The percentages of subjects reporting solicited adverse reactions are shown in the table below.

Table 45: Study V58P4 - Percentage of Subjects with Solicited Adverse Reactions

	Subjects 18-60 Years		Subjects ≥ 61 Years	
	Flucelvax N=652	Agriflu N=648	Flucelvax N=678	Agriflu N=676
Any	40%	41%	34%	32%
Local	32%	31%	22%	18%
Systemic	22%	23%	22%	22%
Other*	7%	7%	7%	6%

*Other is the percentage of subjects who stayed home due to solicited reactions and the percentage of subjects who used analgesic/antipyretic medication

Source: BLA 125408/0, CSR for V58P4, Table 12.2.1.1-1, page 108 and Table 12.2.1.2-1, page 110

The percentages of subjects with any adverse reactions, with local adverse reactions, and with systemic adverse reactions were similar in the two vaccine arms. The percentages of subjects with solicited adverse reactions were lower in elderly subjects than in younger subjects.

Reviewer comment: Lower rates of local solicited adverse reactions in the elderly are commonly observed and are thought to be due to immunosenescence.

The incidence of the individual local solicited reactions is shown in the following table. There were no severe reactions reported for induration, so that category is not included in the table.

Table 46: Study V58P4 - Percentage of Subjects Reporting Individual Local Solicited Adverse Reactions

	Subjects 18-60 Years		Subjects ≥ 61 Years	
	Flucelvax N=652	Agriflu N=648	Flucelvax N=678	Agriflu N=676
Pain				
Any	141 (22%)	111 (17%)	64 (9%)	32 (5%)
Severe	3 (<1%)	2 (<1%)	0	0
Erythema				
Any	92 (14%)	106 (16%)	72 (11%)	72 (11%)
Severe	0	1 (<1%)	0	1 (<1%)
Induration	38 (6%)	42 (6%)	37 (5%)	29 (4%)
Swelling				
Any	25 (4%)	27 (4%)	23 (3%)	17 (3%)
Severe	2 (<1%)	1 (<1%)	1 (<1%)	0
Ecchymosis				
Any	18 (3%)	22 (3%)	26 (4%)	25 (4%)
Severe	0	1 (<1%)	0	0

Source: BLA 125408/0, CSR for V58P4, Table 12.2.3.1-1, page 114 and Table 12.2.3.2-1, page 121

Reviewer comment: The definition of severe adverse reactions was not provided in the Clinical Study Report.

Pain was the most frequently reported solicited local adverse reaction and was observed at a slightly higher percentage in Flucelvax recipients compared Agriflu recipients. The only

other solicited local adverse reaction observed in more than 10% of subjects in either treatment arm or age subgroup was erythema; the percentage of subjects with erythema was similar in the two treatment arms. The percentages of subjects with each individual solicited local adverse reaction were lower in the elderly subgroup compared to in adults 18 to 60 years of age.

Severe solicited local adverse reactions were uncommon and were reported in less than 1% of subjects.

Reviewer comment: Pain at the injection site was the most frequently observed solicited local adverse reaction and was observed slightly more commonly in Flucelvax recipients compared to Agriflu recipients. Erythema was the only other local adverse reaction reported in more than 10% of subjects, but there was no difference in the percentages of subjects with erythema between the two vaccine arms. Severe solicited local adverse reactions were rare.

The percentages of subjects with individual solicited systemic adverse reactions are shown in the following table.

Table 47: Study V58P4 - Number of and Percentage of Subjects Reporting Individual Systemic Solicited Adverse Reactions

	Subjects 18-60 Years		Subjects ≥ 61 Years	
	Flucelvax N=652	Agriflu N=648	Flucelvax N=678	Agriflu N=676
Chills				
Any	25 (4%)	29 (4%)	23 (3%)	26 (4%)
Severe	1 (<1%)	1 (<1%)	0	2 (<1%)
Malaise				
Any	74 (11%)	74 (11%)	70 (10%)	75 (11%)
Severe	4 (1%)	4 (1%)	1 (<1%)	3 (<1%)
Myalgia				
Any	45 (7%)	49 (8%)	46 (7%)	57 (8%)
Severe	1 (<1%)	1 (<1%)	0	3 (<1%)
Arthralgia				
Any	31 (5%)	27 (4%)	41 (6%)	44 (7%)
Severe	0	1 (<1%)	1 (<1%)	3 (<1%)
Headache				
Any	81 (12%)	79 (12%)	69 (10%)	70 (10%)
Severe	2 (<1%)	3 (<1%)	3 (<1%)	5 (1%)
Sweating				
Any	28 (4%)	27 (4%)	44 (6%)	48 (7%)
Severe	1 (<1%)	1 (<1%)	3 (<1%)	4 (1%)
Fatigue				
Any	73 (11%)	73 (11%)	73 (11%)	84 (12%)
Severe	1 (<1%)	1 (<1%)	0	3 (<1%)
Fever				
Any (≥38.0° C axillary)	2 (<1%)	5 (1%)	5 (1%)	5 (1%)
≥ 40.5 ° C	0	0	0	0

Source: BLA 125408/0, CSR for V58P4, Table 12.2.3.1-3, page 116 and Table 12.2.3.2-3, page 123

Myalgia, headache, and fatigue were the only solicited systemic adverse reactions reported in more than 10% of subjects in any treatment arm and were reported in more than 10% of subjects in both vaccine arms and in both age subgroups. There was no solicited systemic adverse reaction reported with more than 5% difference between either vaccine arm.

Severe systemic solicited adverse reactions were reported uncommonly. The incidence of subjects with individual severe systemic adverse reactions was 1% or less in all arms for all adverse reactions.

Fever (defined as axillary temperature $\geq 38.0^{\circ}\text{C}$) was reported in 1% of subjects in both the Flucelvax and Agriflu arms; all events of fever were mild except for one subject in the Agriflu arm with moderate fever. (Moderate fever was defined as axillary temperature of $39.0\text{--}39.9^{\circ}\text{C}$).

Reviewer comment: The percentages of subjects with each individual solicited general adverse reaction was similar in the Flucelvax and the Agriflu arms for both subjects 18 to 60 years of age and 61 years of age and older.

The applicant also collected information on the percentage of subjects who stayed home due to a solicited adverse reaction and the percentage who used analgesics or antipyretics during the seven days after vaccination. The results for these queries are shown in the table below.

Table 48: Study V58P4 - Percentage of Subjects Reporting Other Systemic Solicited Adverse Reactions in the Seven Days Post-Vaccination

	Flucelvax N=652	Agriflu N=648	Flucelvax N=678	Agriflu N=676
Stayed home due to adverse reaction	2%	2%	3%	2%
Analgesic or antipyretic use	7%	6%	5%	4%

Source: BLA 125408/0, CSR for V58P4, Table 12.2.3.1-3, page 116 and Table 12.2.3.2-3, page 123

Reviewer comment: The percentages of subjects who stayed home due to a solicited adverse reaction and the percentages of subjects who used analgesics or antipyretics due to a solicited adverse reaction were similar in the two vaccine treatment arms.

Unsolicited adverse events

Information on unsolicited adverse events was collected for the 21 days post-vaccination. In the 18 to 60 year age group, unsolicited AEs were reported in 14% of subjects who received Flucelvax and in 15% of subjects who received Agriflu. In the 61 year and older age group, unsolicited AEs were reported in 15% of subjects who received Flucelvax and in 13% who received Agriflu. The percentage of subjects with unsolicited adverse events by system organ class when reported in more than 2% of subjects in any treatment arm is shown in the table below.

Table 49: Study V58P4 - Percentage of Subjects with Unsolicited Adverse Events in Specific Organ System Classes (Organ Classes with $\geq 2\%$ of Subjects Reporting an AE)

	Flucelvax N=652	Agriflu N=648	Flucelvax N=678	Agriflu N=676
Any	14%	15%	15%	13%
Infections and Infestations	6%	7%	4%	5%
Respiratory, thoracic, and mediastinal	4%	4%	4%	4%
General / Administrative site	3%	3%	4%	3%
Nervous system disorders	3%	3%	2%	1%
Gastrointestinal disorders	3%	2%	2%	2%
Musculoskeletal, connective tissue, and bone	2%	2%	3%	2%

Source: BLA 125408/0, CSR for V58P4, Table 12.2.3.1-5, page 119 and Table 12.2.3.2-5, page 126

Reviewer comment: The percentage of subjects with unsolicited AEs in each organ system class was low and was similar between the two treatment arms in each age subgroup.

Reviewer comment: On review of the AE dataset, the most frequently reported unsolicited adverse events were rhinitis (45 AEs in the Flucelvax arm and 55 in the Agriflu arm). There were 31 AEs of pharyngolaryngeal pain in the Flucelvax arm and 38 in the Agriflu arm. Other AEs reported frequently were those that were also solicited such as headache (26 AEs in the Flucelvax arm and 24 in the Agriflu arm), arthralgia (17 in the Flucelvax arm and 16 in the Agriflu arm), and malaise (16 in the Flucelvax arm and 11 in the Agriflu arm). No individual solicited adverse event or class of adverse events was reported at an unexpectedly high rate. The majority of unsolicited AEs were consistent with illnesses commonly observed in an adult population. There were no reports of Guillain Barré syndrome or of oculorespiratory syndrome.

Reviewer comment: The datasets were searched for unsolicited adverse events that might have been related to hypersensitivity or allergy related to the study vaccine. The preferred term, hypersensitivity, was not reported. However, one AE of urticaria was reported on Day 6 in a subject who received Agriflu. It was judged as mild and not vaccine related. Five subjects in the Flucelvax arm had rashes in the seven days post-vaccination. One was pruritis and one was macular. One of the five rashes was judged as possibly vaccine related. Four subjects in the Agriflu arm reported rashes; two were judged as possibly vaccine related. No increase in signs and symptoms consistent with an allergic reaction to Flucelvax were observed in this study.

Severe unsolicited adverse events were reported in two subjects in the adult Flucelvax arm (diarrhea and laryngitis) and in three subjects in the Agriflu arm (toothache, otitis media, and headache). Severe unsolicited AEs were reported in 13 elderly subjects: seven subjects in the Flucelvax arm (acute MI, coronary artery disease, benign esophageal neoplasm, lung squamous cell carcinoma, retinal detachment, carbon monoxide poisoning, and procedural complication) and six subjects in the Agriflu arm (unstable angina, atrial fibrillation, vertigo, vomiting, rhinitis, gallbladder cancer, lung adenocarcinoma, cerebrovascular accident, headache, cough, pharyngolaryngeal pain, and hypertensive crisis). None of the severe unsolicited adverse events was judged by the investigators as related to study vaccine.

Study discontinuations due to adverse events

There were three premature study discontinuations. All three were due to death and were in the elderly study population. Please see discussion of deaths in the next section of this review.

6.2.9.6.2 Deaths

There were three deaths in the study. All three were reported in the cohort of subjects 61 years of age and older. One was in the Flucelvax arm and two in the Agriflu arm. None of the deaths were judged by the investigators as related to study vaccination. Narratives for the deaths were not provided but have been requested from the applicant. The deaths are described below.

Subject 032147, a 73 year old male, died 25 days after vaccination with Flucelvax due to carbon monoxide poisoning after helping fight a house fire.

Subject 042009, a 77 year old male in the Agriflu arm with a history of diabetes mellitus, hypertension, coronary heart disease, arteriosclerosis, and aortic aneurysm, died 166 days post-vaccination due to lung adenocarcinoma.

Subject 012259, a 75 year old male in the Agriflu arm with a history of hypertension, hypercholesterolemia, and hyperthyroidism, died 39 days post-vaccination due to a cerebrovascular accident.

Reviewer comment: The study dates on which two of these subjects died differ slightly in the datasets and in the Clinical Study Report. The differences (Day 42 instead of 39 and Day 189 instead of 166) should not have affected study conclusions. Narratives for these deaths have been requested.

In the opinion of this reviewer, none of these deaths appear to be related to the study vaccine.

6.2.9.6.3 Nonfatal Serious Adverse Events

A total of 56 serious adverse events were reported in 47 subjects (1.7%). The majority of SAEs were reported in subjects 61 years of age and older (46 SAEs in 56 subjects). Twelve SAEs were reported in 12 subjects (<1%) in the 18 to 60 year age group: seven subjects in the Flucelvax arm and five in the Agriflu arm. None of the SAEs were judged as vaccine related. The only SAEs reported in more than a single subject were hypoacusis (two Flucelvax subjects and one Agriflu subject) and bronchopneumonia (reported in one subject in each arm). Two SAEs were reported within 30 days of study vaccination: hypoacusis on Day 24 and alcohol poisoning on Day 12; both were reported in subjects who received Flucelvax.

In the elderly, 46 serious AEs were reported. SAEs were reported in 19 subjects who received Flucelvax and in 18 subjects who received Agriflu. Serious adverse events reported in more than two subjects in either arm are shown in the following table.

Table 50: Study V58P4 - Number of Subjects 61 Years of Age and Older with Serious Adverse Events (≥ 2 Subjects in Any Arm)

	Flucelvax N=678	Agriflu N=676
Atrial fibrillation	2	3
Pneumonia / bronchopneumonia	2	2
Myocardial infarction	2	1
Coronary artery disease	2	0
Unstable angina / angina	0	3

Source: BLA 125408/0, CSR V58P4, Table 12.3.1.2-2, pages 133-135

Reviewer comment: The number of SAEs reported varied in the tabular listing in the CSR and in the datasets for AEs; there were three additional SAEs reported in the CSR that were not included in the datasets. This did not change the conclusions regarding safety.

Four SAEs were reported within 30 days of vaccination. There were three SAEs in the 30 days post-vaccination in the Flucelvax arm: atrial fibrillation on Day 6, pneumonia on Day 19, and lung squamous cell carcinoma on Day 28. There was one SAE within 30 days of vaccination in the Agriflu arm: an inner ear disorder on Day 9.

None of the SAEs were judged by the investigator to be vaccine related.

Reviewer comment: The incidence of individual serious AEs was less than 1% in both the Flucelvax and the Agriflu arms. In the elderly population, the majority of SAEs were cardiac disorders, but the number of subjects with cardiac SAEs was similar in the two arms (eight in the Flucelvax arm and six in the Agriflu arm), no individual type of cardiac SAE was predominant, and all but one cardiac SAE was reported more than 30 days post-vaccination. In the opinion of this reviewer, none of these serious AEs were likely to be related to the study vaccines.

There were three pregnancies during the six month follow-up period of this study: two in the Flucelvax arm and one in the Agriflu arm. Two pregnancies resulted in healthy newborns. A 21 year old female gave birth to a live newborn without congenital anomalies 11 months after receiving Flucelvax. A 22 year old female gave birth to a live newborn without congenital anomalies 13 months after receipt of Agriflu. One pregnant woman in the Flucelvax arm was lost to follow-up.

6.2.10 Comments & Conclusions

The antibody response to Flucelvax was non-inferior to that to a US-licensed vaccine, therefore, the results of this study provide the basis to infer effectiveness of Flucelvax in individuals 50 years of age and older. Although this study was stratified by ages 18 to 60 years and 61 years of age and older, the results were re-analyzed to meet the definition of elderly used by FDA for influenza vaccines (65 years and older). This re-analysis is more appropriate for inclusion in the package insert for the US. The most commonly reported solicited adverse reactions were pain and erythema at the injection site, headache, fatigue, and malaise. There was no increase in individual unsolicited AE, serious AE, or cause of death or in adverse events in an organ system observed in this study. In conclusion, the results of this study provide the primary support for the immunogenicity and safety of Flucelvax in elderly subjects.

6.3 Trials #3 Study V58P4E1

Study V58P4E1 was a six month extension study of Study V58P4. Subjects who had completed study V58P4 were invited to enroll in V58P4E1. Subjects were stratified by age at the time of enrollment into V58P4 and by vaccine received in Study V58P4. Subjects were re-randomized in a 1:1 ratio to receive a single 0.5 mL dose of Flucelvax or Agriflu in the deltoid muscle of the non-dominant arm. As a result, there were four vaccine arms for each age subgroup (adults 18 to 60 years of age and elderly subjects 61 years of age and older) based on vaccines received in V58P4 and V58P4E1: Flucelvax/Flucelvax, Flucelvax/Agriflu, Agriflu/Agriflu, and Agriflu/Flucelvax.

The study design for V58P4E1 was almost identical to that of Study V58P4. Differences in Study V58P4E1 included the following:

- The influenza strains included in the study vaccines in V58P4E1 were those recommended for the 2005-2006 influenza season in the Northern Hemisphere. The H1N1 and B strains were identical to the ones used in Study V58P4, but the H3N2 strain was changed to A/California/7/2004.
- Because of the stratification by age and previous study vaccine, four randomization lists were used at each site.
- Antibody titers were obtained in a subgroup of 480 subjects, 240 in each age subgroup. The immunogenicity subset was defined as the first 120 subjects who enrolled in each age subgroup at study centers 01 and 05.
- Information on AEs resulting in a physician's visit was collected for six months post-vaccination.
- No non-inferiority comparison of Flucelvax to Agriflu was planned.

Reviewer comment: Since two of the influenza strains contained in the study vaccines in V58P4E1 were identical to those in the study vaccines in V58P4, vaccination in Study V58P4E1 was similar to providing a booster dose to subjects who had previously been vaccinated.

The usefulness of the study results is limited for the following reasons; 1) One could expect high baseline titers for the two identical vaccine strains and as a result, seroconversion rates and geometric mean titers might be lower than if subjects were vaccinated with new influenza strains.. 2) Influenza vaccine is recommended yearly without consideration of the vaccine(s) previously received. 3) More than 15% of subjects chose not to enroll in the extension study. 4) Antibody titers were analyzed for a subset of re-vaccinated subjects only. For these reasons, the results will only be described briefly.

6.3.1 Study Population and Disposition

Study V58P4E1 was conducted at the same 5 study sites in Poland as V58P4.

6.3.2 Populations Enrolled/Analyzed and Subject Disposition

Of the 2,654 subjects in Study V58P4, 2,235 subjects (84%) were re-vaccinated in Study V58P4E1. This included 1105 subjects (83%) from the Flucelvax arm and 1130 (85%) from the Agriflu arm in Study V58P4.

6.3.3 Immunogenicity Analyses

As in Study V58P4, HAI antibody titers from subjects in Study V58P4E1 were analyzed using seroconversion rate, percentage of subjects with HAI titers of 1:40 or greater post-vaccination, and geometric mean ratio. Protocol-defined success criteria were outlined in EMA /CHMP recommendations:

Point estimate for seroconversion rate for adults $\geq 40\%$ and for elderly $\geq 30\%$.

Point estimate for percentage of subjects with post-vaccination HAI titer $\geq 1:40$ of $\geq 70\%$ for adults and $\geq 60\%$ for elderly, and

Point estimate for GMR for adults ≥ 2.5 and for elderly ≥ 2.0 .

Immunogenicity results for the 18 to 60 year age group are shown in the following table.

Table 51: Study V58P4E1 - Results (Point Estimates) for Seroconversion Rate, Percentage of Subjects with HAI Titers $\geq 1:40$, and Geometric Mean Ratio in Subjects 18 to 60 Years of Age who Received Flucelvax in Study V58P4E1 (Per Protocol Population)

Vaccine Received in V58P4 /V58P4E1	Flucelvax / Flucelvax N=60			Agriflu / Flucelvax N=60		
	H3N2	H1N1	B	H3N2	H1N1	B
SCR	82%	22%	28%	80%	30%	40%
% $\geq 1:40$ Baseline	25%	57%	50%	33%	57%	58%
% $\geq 1:40$ Day 22	92%	85%	80%	92%	90%	87%
GMR	11	2.14	2.61	8.05	2.91	2.93

Source: BLA 125408/0, CSR for V58P4E1, Tables 11.4.1.1.1-1 to 11.4.1.1.1-3, pages 73-75

Table 52: Study V58P4E1 - Results (Point Estimates) for Seroconversion Rate, Percentage of Subjects with HAI Titers $\geq 1:40$, and Geometric Mean Ratio in Subjects 18 to 60 Years of Age who Received Agriflu in Study V58P4E1 (Per Protocol Population)

Vaccine Received in V58P4 /V58P4E1	Flucelvax / Agriflu N=59			Agriflu / Agriflu N=60		
	H3N2	H1N1	B	H3N2	H1N1	B
SCR	85%	32%	33%	61%	24%	27%
% $\geq 1:40$ Baseline	27%	48%	50%	32%	54%	54%
% $\geq 1:40$ Day 22	95%	80%	90%	86%	80%	85%
GMR	6.17	2.46	2.7	4.09	2.02	1.81

Source: BLA 125408/0, CSR for V58P4E1, Tables 11.4.1.1.1-1 to 11.4.1.1.1-3, pages 73-75

The EMA / CHMP criteria for demonstration of immunogenicity were met for both Flucelvax and for Agriflu.

Reviewer comment: The percentage of subjects with HAI titers of 1:40 or higher were approximately 50% against the two influenza strains that had also been in the vaccine used in the previous study. As a result, the fold increases in these titers and the seroconversion rates were lower compared to the antibody response to the H3N2 strain.

Since antibody titers were obtained only for a subset of subjects, the confidence intervals, which are not shown in this review, were wider in V58P4E1 than in V58P4.

Immunogenicity results for the 61 years of age and older age group are shown in the following table.

Table 53: Study V58P4E1 - Results (Point Estimates) for Seroconversion Rate, Percentage of Subjects with HAI Titers $\geq 1:40$, and Geometric Mean Ratio in Subjects ≥ 61 Years of Age who Received Flucelvax in Study V58P4E1 (Per Protocol Population)

Vaccine Received in V58P4 /V58P4E1	Flucelvax / Flucelvax N=60			Agriflu / Flucelvax N=60		
	H3N2	H1N1	B	H3N2	H1N1	B
SCR	84%	30%	28%	82%	43%	41%
% $\geq 1:40$ Baseline	30%	49%	59%	34%	48%	62%
% $\geq 1:40$ Day 22	97%	77%	84%	92%	82%	90%
GMR	12	2.2	2.37	12	3.11	3.19

Source: BLA 125408/0, CSR for V58P4E1, Tables 11.4.1.1.2-1 to 11.4.1.1.2-3, pages 76-78

Table 54: Study V58P4E1 - Results (Point Estimates) for Seroconversion Rate, Percentage of Subjects with HAI Titers $\geq 1:40$, and Geometric Mean Ratio in Subjects ≥ 61 Years of Age who Received Agriflu in Study V58P4E1 (Per Protocol Population)

Vaccine Received in V58P4 /V58P4E1	Flucelvax / Agriflu N=60			Agriflu / Agriflu N=59		
	H3N2	H1N1	B	H3N2	H1N1	B
SCR	80%	34%	34%	77%	30%	31%
% $\geq 1:40$ Baseline	39%	36%	61%	29%	36%	43%
% $\geq 1:40$ Day 22	95%	74%	92%	87%	69%	84%
GMR	7.64	2.98	2.67	6.59	2.54	2.64

Source: BLA 125408/0, CSR for V58P4E1, Tables 11.4.1.1.2-1 to 11.4.1.1.2-3, pages 76-78

The EMA / CHMP criteria were also met for both vaccines in the 61 years of age and older subgroup.

6.3.4 Safety Analyses

All of the study subjects were vaccinated and all are included in at least one of the safety analysis. The safety results are shown by vaccine received in Study V58P4E1.

6.3.4.1 Non-Serious Adverse Events

Solicited adverse reactions

Solicited adverse reactions were followed for the seven days after vaccination. The percentages of subjects reporting solicited adverse reactions are shown in the table below.

Table 55: Study V58P4E1 - Percentage of Subjects with Solicited Adverse Reactions

	Subjects 18-60 Years		Subjects ≥ 61 Years	
	Flucelvax N=533	Agriflu N=534	Flucelvax N=571	Agriflu N=597
Any	36%	33%	26%	25%
Local	30%	28%	18%	16%
Systemic	16%	16%	15%	13%
Other*	5%	4%	3%	3%

*Other is the percentage of subjects who stayed home due to solicited reactions and the percentage of subjects who used analgesic/antipyretic medication

Source: BLA 125408/0, CSR for V58P4E1, Table 12.2.1.1-1, page 98 and Table 12.2.1.2-1, page 103

The percentages of subjects with any adverse reactions, with local adverse reactions, and with systemic adverse reactions were similar in the two vaccine arms. The percentages of subjects with each of the adverse reactions were slightly lower than in V58P4. As in V58P4, the percentages of subjects with solicited adverse reactions were lower in elderly subjects than in younger subjects.

The incidence of the individual local solicited reactions is shown in the following table. There were no severe reactions reported for ecchymosis, so that category is not included in the table.

Table 56: Study V58P4E1 - Percentage of Subjects Reporting Individual Local Solicited Adverse Reactions

	Subjects 18-60 Years		Subjects ≥ 61 Years	
	Flucelvax N=533	Agriflu N=534	Flucelvax N=571	Agriflu N=597
Pain				
Any	115 (22%)	91 (17%)	48 (8%)	40 (7%)
Severe	3 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Erythema				
Any	59 (11%)	66 (12%)	46 (8%)	35 (6%)
Severe	0	0	3 (1%)	0
Induration				
Any	35 (7%)	31 (6%)	24 (4%)	17 (3%)
Severe	1 (<1%)	2 (<1%)	0	0
Swelling				
Any	17 (3%)	16 (3%)	15 (3%)	9 (2%)
Severe	1 (<1%)	1 (<1%)	3 (1%)	0
Ecchymosis	26 (5%)	24 (4%)	23 (4%)	33 (6%)

Source: BLA 125408/0, CSR for V58P4E1, Table 12.2.3.1-1, page 111 and Table 12.2.3.2-1, page 125

Pain and erythema were the only solicited local adverse reaction observed in more than 10% of subjects in either treatment arm or age subgroup. Overall, the percentages of subjects with each individual solicited local adverse reaction were lower in the elderly subgroup compared to in adults 18 to 60 years of age. Severe solicited local adverse reactions were uncommon and were reported in less than 1% of subjects.

Reviewer comment: Pain at the injection site was the most frequently observed solicited local adverse reaction and was observed slightly more commonly in Flucelvax adult recipients compared to Agriflu recipients.

The percentages of subjects with individual solicited systemic adverse reactions are shown in the following table.

Table 57: Study V58P4E1 - Number of and Percentage of Subjects Reporting Individual Systemic Solicited Adverse Reactions

	Subjects 18-60 Years		Subjects ≥ 61 Years	
	Flucelvax N=533	Agriflu N=534	Flucelvax N=571	Agriflu N=597
Chills				
Any	15 (3%)	8 (1%)	18 (3%)	12 (2%)
Severe	1 (<1%)	0	2 (<1%)	0
Malaise				
Any	47 (9%)	38 (7%)	48 (8%)	39 (7%)
Severe	2 (<1%)	0	1 (<1%)	1 (<1%)
Myalgia				
Any	38 (7%)	42 (8%)	34 (6%)	19 (3%)
Severe	3 (1%)	0	2 (<1%)	1 (<1%)
Arthralgia				
Any	21 (4%)	16 (3%)	29 (5%)	25 (4%)
Severe	2 (<1%)	0	1 (<1%)	3 (1%)
Headache				
Any	51 (10%)	42 (8%)	36 (6%)	37 (6%)
Severe	4 (1%)	0	3 (1%)	3 (1%)
Sweating				
Any	23 (4%)	19 (4%)	26 (5%)	17 (3%)
Severe	2 (<1%)	0	1 (<1%)	2 (<1%)
Fatigue				
Any	41 (8%)	42 (8%)	48 (8%)	40 (7%)
Severe	3 (1%)	1 (<1%)	0	1 (<1%)
Fever				
Any (≥38.0° C axillary)	2 (<1%)	5 (1%)	2 (<1%)	2 (<1%)
≥ 40.5 ° C	0	0	0	0

Source: BLA 125408/0, CSR for V58P4E1, Table 12.2.3.1-3, page 108 and Table 12.2.3.2-3, page 123

Headache was the only solicited systemic adverse reactions reported in more than 10% of subjects in any treatment arm and were reported in 10% of subjects in the adult Flucelvax arm only. Severe systemic solicited adverse reactions were reported uncommonly.

Reviewer comment: The percentages of subjects with each individual solicited general adverse reaction was similar in the Flucelvax and the Agriflu arms for both subjects 18 to 60 years of age and 61 years of age and older. There was a slight increase in the number of subjects with severe solicited systemic adverse reactions in the adult Flucelvax arm compared to the adult Agriflu arm, but the percentage of the subjects with severe adverse reactions in the Flucelvax arm was very low.

Unsolicited adverse events

Unsolicited adverse events were reported in 18% of adult subjects who received Flucelvax, 14% of adult subjects who received Agriflu, 26% of elderly subjects who received Flucelvax, and 21% of elderly subjects who received Agriflu. The only system organ class in which more than 5% of subjects in any treatment arm reported unsolicited adverse events was Infections and Infestations. In the adult subgroup, 10% of Flucelvax recipients and 7% of Agriflu recipients had an AE from this system organ class. In the elderly subgroup, 12% of Flucelvax recipients and 9% of Agriflu recipients had an AE from this system organ class

Reviewer comment: The percentages of subjects with unsolicited AEs in each organ system class were low and similar between the two treatment arms in each age subgroup.

Reviewer comment: On review of the AE dataset, the most frequently reported unsolicited adverse events were rhinitis, pharyngeal pain, and bronchitis. The majority of unsolicited AEs were consistent with illnesses commonly observed in an adult population.

There were no reports of Guillain Barré syndrome or of oculorespiratory syndrome. The datasets were searched for unsolicited adverse events that might have been related to hypersensitivity or allergy related to the study vaccine. No AEs of hypersensitivity, allergic reaction, urticaria, or rash were reported in Flucelvax or in Agriflu recipients.

Study discontinuations due to adverse events

There were a total of six premature study discontinuations. Two, one in each vaccine arm, were due to acute myocardial infarction. The other four were associated with subject deaths; please see discussion of deaths in the next section of this review.

6.3.4.2 Deaths

There were five deaths in the study. None of the deaths were judged by the study investigator as vaccine related. The deaths in the Flucelvax arm are described below.

Subject 010128 was a 57 year old male who committed suicide five days after vaccination.

Subject 012152 was a 74 year old male who suffered a gastrointestinal hemorrhage on Day 52 then died of an acute myocardial infarction 61 days post-vaccination.

Subject 052148 was a 88 year old male with a history of coronary artery disease who died of sudden cardiac death 35 days post-vaccination.

The following subjects in the Agriflu arm died during study participation.

Subject 012554 was a 77 year old male who died of a cerebral hemorrhage 129 days after receiving Agriflu.

Subject 012221 was a 77 year old female who died of necrotizing pancreatitis and peritonitis 59 days post-vaccination.

Reviewer comment: In the opinion of this reviewer, none of these deaths appear to be related to the study vaccine.

6.3.4.3 Nonfatal Serious Adverse Events

A total of 87 serious adverse events were reported in 66 subjects. The percentages of adults 18 through 60 years with SAEs were 2% in the Flucelvax arm and 1% in the Agriflu arm; the percentages of subjects with SAEs in subjects 61 years of age and older were 4% in the Flucevax arm and 5% in the Agriflu arm. Six SAEs were reported more than once in the Flucelvax arm: acute myocardial infarction/ myocardial infarction, which was reported five times; chest pain, which were reported three times; and Adam Stokes syndrome, joint contracture, myocardial infarction, and varicose vein, which were each reported twice. In the Agriflu arm, three SAEs were reported more than once: cholelithiasis, which was reported four times, atrial fibrillation and forearm fracture, which were each reported twice. None of the SAEs were judged as vaccine related.

Eleven SAEs were reported within 30 days of vaccination: eight in the Flucelvax arm and three in the Agriflu arm. The eight SAEs in the Flucelvax arm were chest pain (reported in two subjects on Days 2 and 14), acute myocardial infarction (reported in two subjects on Days 4 and 13), suicide (Day 5), atrial fibrillation (Day 13), joint contracture (Day 4), and knee replacement (Day 25). Four SAEs were reported in three subjects in the Agriflu arm within 30 days of vaccination; these included one subject with atrial fibrillation on Day 12, one subject with an acute MI on Day 13, and one subject with an open forearm fracture on Day 8. None of the SAEs were judged as vaccine related.

Reviewer comment: Serious adverse events were uncommon in adults and in the elderly.

There were three pregnancies during the six month follow-up period of this study: all three were in the Agriflu arm. Two pregnancies resulted in healthy newborns and the third mother was lost to follow-up.

6.3.5 Comments & Conclusions

In this extension study, 84% of subjects in Study V58P4 were re-randomized and vaccinated with a second dose of influenza vaccine. The usefulness of these results are limited due to the loss of subjects from the first study and the inclusion of two identical influenza strains in both studies. However, there were no increases in any individual adverse event or class of adverse events observed in Flucelvax recipients compared to Agriflu recipients.

6.4 Trials #4 Study V58P9

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

6.4.1 Objectives

The primary safety objectives were:

- to evaluate the safety and tolerability of Flucelvax as compared to Agriflu three weeks after a single dose of study vaccine, and
- to collect additional safety data such as SAEs, medically attended AEs, and AEs resulting in premature study discontinuation for six months post-vaccination.

Reviewer comment: Although there were safety *and* immunogenicity objectives, the applicant states in the Clinical Study Report that the study was “primarily designed to descriptively assess safety.”

The primary immunogenicity objective was to evaluate the immunogenicity of the two study vaccines and of each vaccine lot three weeks after a single 0.5 mL intramuscular injection, by the measurement of strain-specific HAI tests according to the current CHMP criteria (CPMP/BWP/214/96).

Reviewer comment: This study included three lots of Flucelvax but was not designed as a lot consistency study. Neither the objectives nor the statistical plan addressed lot comparisons. However, the results were re-analyzed for lot consistency post-hoc, and the study results were submitted as supportive of the clinical lot consistency of the three lots of Flucelvax.

6.4.2 Design Overview

Study V58P9 was a Phase 3, observer-blind safety and immunogenicity study of Flucelvax compared to Agriflu in healthy volunteers 18 to 60 years of age. Subjects were randomized in a 2:2:2:1 ratio to one of three lots of Flucelvax or to Agriflu.

Subjects received a single, 0.5mL dose of study vaccine in the deltoid muscle, preferably of the non-dominant arm. Subjects were monitored in the study clinic for 30 minutes post-vaccination. During that time they were provided with diary cards to collect information on adverse reactions to study vaccine for the day of vaccination and the subsequent six days. (See safety monitoring section of this review).

Serum was collected pre-vaccination and on Days 22 and 181 for determination of antibody response to study vaccine.

6.4.3 Population

Study subjects were healthy adult volunteers 18 to < 61 years of age.

Reasons for exclusion from the study included the following:

- laboratory-confirmed influenza disease receipt of an influenza vaccine within the previous 6 months,
- history of hypersensitivity to any component of the study vaccine or to chemically related substances,
- history of any anaphylaxis, serious vaccine reactions, or allergy to any of the vaccine components,

- acute infectious or respiratory disease within five days of enrollment,
- any serious disease such as cancer, autoimmune disease, impaired immune function, advanced arteriosclerotic disease, complicated diabetes mellitus, COPD requiring oxygen therapy, CHF, bleeding diathesis, hepatic disease, or renal disease, or
- participation in another clinical study of an investigational agent within 90 days of study entry or planned for during the safety follow-up period of V58P9.

6.4.4 Study Treatments or Agents Mandated by the Protocol

Study subjects received a single, 0.5 mL dose of study vaccine intramuscularly in the deltoid muscle of the non-dominant arm; study vaccines were Flucelvax (cell-derived vaccine) and Agriflu (egg-derived vaccine). Flucelvax and Agriflu contained 15 µg of HA for each of the strains that were recommended for the 2005-2006 influenza season in the Northern Hemisphere:

6.4.5 Sites and Centers

Study V58P4 was conducted at two study sites in Lithuania. The study was not conducted under US IND.

6.4.6 Surveillance/Monitoring

Subjects were seen at the study centers on Days 1, 22, and 181.

A medical history and physical examination were performed on all subjects on Day 1, prior to vaccination. Physical examinations were repeated at the Days 22 and 181 visit.

Subjects received a single, 0.5 mL dose of study vaccine in the deltoid muscle of the non-dominant arm on Day 1 and remained in clinic for 30 minutes after vaccination to monitor for any immediate reactions. Subjects were discharged with a Diary Card and instructed to record all AEs and solicited adverse reactions for the six days post-vaccination as well as information on all unsolicited AEs until Study Day 22. Diary Cards were collected at the Day 22 visit. Information on serious AEs, medically attended AEs, AEs that resulted in study withdrawal, and pregnancies was collected for the 180 days post-vaccination.

6.4.7 Endpoints and Criteria for Study Success

The primary safety endpoints were adverse events collected as solicited adverse reactions in the seven days post-vaccination, all unsolicited adverse events for the 21 days post-vaccination, and serious adverse events and serious AEs, medically attended AEs, and AEs resulting in premature study discontinuation for the 180 days post-vaccination.

The primary immunogenicity endpoint was the antibody response after a single dose of study vaccine for each vaccine influenza strain. Antibody titers were measured pre-vaccination and on Day 22 post-vaccination.

6.4.8 Statistical Considerations & Statistical Analysis Plan

Subjects were randomized in a 2:2:2:1 ratio to receive a single dose of one of three lots of Flucelvax or to Agriflu. One randomization list was prepared by Chiron (now Novartis)

Biostatistics and Clinical Data Management Department for each of the two study sites. The study was observer-blind, i.e., designated study personnel who administered the study vaccine had no further contact with the study subject, and study personnel involved with subsequent procedures were blinded to treatment assignment.

Antibody responses were assessed by seroconversion rate at Day 22, the percentage of subjects with HAI titer $\geq 1:40$ at Day 1 and at Day 22, the geometric mean titers at Day 1 and at Day 22, and the Day 22/Day 1 geometric mean ratio

The sample size was based on recommendations from the EMA about the size of the safety database needed for licensure of Flucelvax.

Reviewer comment: In the Clinical Study Report, the applicant states that the study was designed primarily to provide a descriptive assessment of safety and not as a lot consistency study.

The criteria for assessment of lot consistency were not included in the study protocol but were defined post-hoc after immunogenicity results were known.

Reviewer comment: The study was not designed to examine lot consistency, but post-hoc analyses for lot consistency were conducted after the results were known to the applicant. In the opinion of the reviewer, a strong potential for bias exists due to the study conduct. In addition, the use of results from a post-hoc analysis in a study to support effectiveness is discouraged because of the risk of bias, as described in the FDA Guidance for Industry, "Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products." Post-hoc analyses are also discouraged because of multiplicity concerns described in FDA Guidance for Industry, "E9 Statistical Principles for Clinical Trials."

6.4.9 Results

The study results are not presented because of issues with the study conduct as summarized as follows:

Study V58P9 was conducted at two study sites in Lithuania: Site 1 was the Vilnius Hospital, and Site 2 was the Panevezys Hospital. The study began in September 2005 and was completed in April 2006. In February, 2007, approximately 10 months after Study V58P9 was completed, the regulatory agency of Lithuania (SMCA) began an investigation of Site 2 because of issues with a separate Novartis study (V87P4) started at Site 2 in February 2007. Site 2 had been audited by Chiron in November 2005 and by Novartis in 2006. SMCA inspected Site 2 in February and in March of 2007 and then issued a final report on their findings at Site 2 on March 8, 2007. The Lithuanian regulatory authorities concluded that the trial (V87P4), due to the fault of the investigators, did not meet the laws of the Republic of Lithuania or the requirements of Good Clinical Practice, and violated the regulations of the Helsinki declaration. In addition, the SMCA concluded that one of the investigators "purposely misled" the inspectors and the SMCA. As a result, criminal charges of fraud were brought against this investigator and criminal charges of forgery were brought against an additional investigator. Of note, these charges were in connection with study V87P4 and **not** V58P9. Novartis subsequently re-audited site 2 in March 2007 and concluded that although the audit did result in evidence of "suboptimal" quality of some of the activities at site 2 during the Flucelvax study, there was no evidence to conclude that data from

study site 2 should be “disqualified.” This reviewer disagrees with the applicant’s conclusions, and remains concerned about the results from the applicant’s audit of study site 2 for several reasons including a) enrollment of a large number of subject in a short amount of time (average 83/day) with only one blood sampling nurse also in charge of packaging samples for shipping, b) body temperatures all ranged with 0.9C, c) 6.8% of diary cards had inconsistent writing. Thus, in the opinion of this reviewer, the site conducted the study in a manner that was not consistent with Good Clinical Practice, and the validity of the results from Site 2 in Study V58P9 cannot be assured.

Note there were only 2 study sites for V58P9; 500 subjects (52%) were enrolled at site 2 and 700 subjects (58%) were enrolled at site 1. Site 1 was not investigated by the Lithuanian regulatory authority and was not audited by the applicant after the issues with site 2 were discovered. However, because of concerns with site 2, the applicant submitted additional analysis of the results at site 1 only.

The reviewer is questioning study conduct at Site 1 for the following reasons:

- The principal investigator at Site 2, who was subsequently arrested for misconduct and forgery, was a sub-investigator at Site 1.
- More than 100 subjects were enrolled per day at Site 2.
- There were 24 pairs of subjects with the same date of birth and same gender, indicating that some subjects may have enrolled twice at Site 1.
- There was no additional audit of Site 1 by the sponsor after the issues at Site 2 were discovered.
- Analysis of data from Site 1 only raises concerns about using results from 58% of subjects enrolled in the study while censoring data from 42% of subjects.

In summary, in the opinion of this reviewer, it is not appropriate to use the results from Site 1 because of the concerns with study conduct at Site 1, the lack of thorough auditing at Site 1, the use of post hoc analysis performed after antibody titers were known to the applicant, and the possibility of introducing bias when the study conclusion is the 58% of the data. Therefore, clinical lot consistency was not demonstrated in the study and the results of this study cannot be included in the package insert and were not described in this review.

6.5 Phase 1 and Phase 2 Studies

Results of three Phase 1 and/or Phase 2 studies were submitted to support the safety and immunogenicity of Flucelvax. These results of these studies will be described briefly.

Of note, clinical laboratory safety monitoring was performed in one of the Phase 1 studies (V58P1) and in a Phase 2 study (V58P5) only. These laboratory results will be discussed in Section 8.4.5 of this review.

6.5.1 Trial #5 Study V58P1

Study Title: A Phase 1/2, observer-blind, randomized, single-center, sequential cohort 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 V58P1 compared Flucelvax and Agriflu in two age subgroups: 18 to 60 years and ≥ 61 years of age. An initial cohort of subjects (N=40) were enrolled and evaluated for safety before the majority of subjects were enrolled and vaccinated in the second cohort. Subjects received a single 0.5 mL intramuscular dose of study vaccine on Day 1 and were followed for 21 days post-vaccination. Information on solicited adverse reactions was collected for seven days post-vaccination, and information on all adverse events was collected for 21 days post-vaccination. Blood samples were obtained on Days 1 and 22 for antibody titers. Antibody response was analyzed by calculation of GMTs, seroconversion rate, percentage of subjects with post-vaccination HAI titers of 1:40 or higher, and GMR. All statistical analyses were descriptive.

Reviewer comment: The immunogenicity results were affected by the pipetting issues described previously in this review. Antibody titers were not re-assayed for this study. For this reason, the applicant did not include the immunogenicity results in the Integrated Summary of Efficacy or in the draft package insert. Therefore, the immunogenicity results will not be discussed in this review.

A total of 240 subjects were enrolled: 122 subjects were 18 to 60 years of age (of these, 60 received Flucelvax and 62 received Agriflu) and 118 were ≥ 61 years of age (of these, 60 received Flucelvax and 58 received Agriflu). The safety results for solicited adverse reactions were similar to those observed in other studies of Flucelvax. Unsolicited adverse events were illnesses frequently observed in adults. There was a single serious adverse event; a 79 year old male in the Flucelvax arm was hospitalized due to syncope in Day 17. The SAE was judged by the investigator as unrelated to study vaccine.

Reviewer comment: The adverse event dataset for this study was reviewed. No reports of anaphylaxis, hypersensitivity, urticaria, or rash were noted in subjects who received Flucelvax. Two subjects reported mild paresthesias on the day of vaccination with Flucelvax. Both AEs were considered possibly related to the study vaccine by study investigators.

6.5.2 Trial #6 Study V58P2

Study Title: A Phase 2, 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

In this study, enrollment of subjects was stratified by age cohort (18 to 60 years and 61 years and older) and randomized in a 1:1 ratio to receive a single 0.5 mL intramuscular dose of Flucelvax or Agriflu. Information on solicited adverse reactions was collected for seven days post-vaccination, and information on all other adverse events was collected for 21 days post-vaccination. Blood samples for antibody response were obtained pre-vaccination and on Day 22. Antibody response was analyzed by calculation of GMTs, seroconversion rate, percentage of subjects with post-vaccination HAI titers of 1:40 or higher, and GMR. Immunogenicity results were evaluated by the CPMP criteria (CPMP/BWP/214/96). All HAI assays were performed using egg-derived antigens. Immunogenicity results are shown in the following table.

Table 58: Results (Point Estimates) for Seroconversion Rate, Percentage of Subjects with HAI Titers $\geq 1:40$, and Geometric Mean Ratio in Subjects 18 to 60 Years of Age (Per Protocol Population)

	Flucelvax N=56			Agriflu N=57		
	H3N2	H1N1	B	H3N2	H1N1	B
SCR	39%	25%	38%	30%	37%	28%
% $\geq 1:40$ Day 1	71%	52%	5%	81%	40%	2%
% $\geq 1:40$ Day 22	95%	77%	46%	96%	79%	39%
GMR	3.38	2.39	3.01	2.5	4.41	2.92

Source: BLA 125408/0, CSR for V58P2, Tables 11.4.1.1-1 to 11.4.1.1-3, pages 69-75

According to the CPMP criteria, one of the three endpoints must be met for each strain (e.g., seroconversion rate $> 40\%$, percentage with post-vaccination HAI titer of 1:40 or greater $> 70\%$, or GMR > 2.5). These criteria were met in this study.

Reviewer comment: The low seroconversion rates observed after vaccination with the influenza A antigens were most likely related to the high antibody titers present at baseline. The majority of adult subjects (82% in the Flucelvax arm and 72% in the Agriflu arm) had previously received an influenza vaccine). However, the seroconversion rates and percentage of subjects with post-vaccination HAI titers of 1:40 or higher at baseline and at Day 22 were all lower to the influenza B strain. The antibody response to influenza B did meet the CPMP criteria demonstration of immunogenicity due to GMR greater than 2.5 in both the Flucelvax and Agriflu arm.

Table 59: Results (Point Estimates) for Seroconversion Rate, Percentage of Subjects with HAI Titers $\geq 1:40$, and Geometric Mean Ratio in Subjects ≥ 61 Years of Age (Per Protocol Population)

	Flucelvax N=54			Agriflu N=56		
	H3N2	H1N1	B	H3N2	H1N1	B
SCR	30%	9%	37%	13%	13%	30%
% $\geq 1:40$ Day 1	76%	69%	4%	82%	57%	4%
% $\geq 1:40$ Day 22	94%	81%	43%	93%	75%	38%
GMR	2.62	1.59	2.96	1.66	1.69	2.76

Source: BLA 125408/0, CSR for V58P2, Tables 11.4.1.2-1 to 11.4.1.2-3, pages 78-84

The CPMP criteria for demonstration of immunogenicity were also met for the elderly cohort.

Reviewer comment: The majority of elderly subjects (94% in the Flucelvax arm and 96% in the Agriflu arm) had previously been vaccinated against influenza. As a result, the percentage of subjects with baseline HAI titers $\geq 1:40$ was high for the influenza A

subtypes, and the seroconversion rate was low. However, antibody response to the influenza B strain was lower than to the A subtypes after both study vaccines; lower antibody responses to influenza B have been observed with other studies of influenza vaccines (see package inserts for FluLaval and Fluzone).

Safety: The percentages of subjects with solicited adverse reactions were similar in the Flucelvax and Agriflu arms both in < 60 year olds and in the older age groups. The percentage of subjects reporting unsolicited AEs was lower in the Flucelvax arm than in the Agriflu arm. The most commonly observed unsolicited AEs were illnesses that are often reported in an adult population such as headache and upper respiratory tract infection. There were no deaths, no serious adverse events, and no adverse events leading to premature study discontinuation.

Reviewer comment: On review of the adverse events dataset, there were no AEs consistent with an allergic reaction (hypersensitivity, urticaria, rash). In addition, Guillain Barré syndrome was not reported.

6.5.3 Trial #7 Study V58P5

Study Title: A Phase 2, observer-blind, randomized, multicenter study in healthy adults to evaluate safety and tolerability and to compare immunogenicity of a single dose of either an investigational trivalent inactivated influenza vaccine produced in mammalian cell culture or a US-licensed trivalent inactivated influenza vaccine (Fluvirin®) produced in embryonated hen eggs

Reviewer comment: This was the only Phase 1 or 2 study of Flucelvax that was conducted in the United States and the first conducted under US IND.

Study V58P5 was an observer-blind, safety, and immunogenicity study of Flucelvax and Fluvirin in healthy adults from 18 to <50 years of age. Enrollment was stratified by age group (18 to ≤ 30, 31 to ≤ 40, and 41 to <50 years of age) and then randomized in a 1:1 ratio to receive a single 0.5 mL intramuscular dose of Flucelvax or Fluvirin on Day 1 of the study. Blood samples were obtained pre-vaccination and on Day 22. The primary objective of the study was to demonstrate immunologic non-inferiority of Flucelvax to Fluvirin; non-inferiority would be demonstrated if the lower limit of the 95% confidence interval around the ratio of the post-vaccination GMTs (Flucelvax/Fluvirin) for each strain was greater than 0.5.

Safety was monitored by collection of information on solicited adverse reactions for the seven days post-vaccination, on unsolicited AEs for seven days post-vaccination, and on serious adverse events and AEs leading to premature study discontinuation for the entire 181 day study period.

Reviewer comment: The study was unique compared to other studies in the BLA in that solicited adverse reactions included signs and symptoms of oculorespiratory syndrome (cough, wheezing, chest tightness, difficulty breathing, sore throat, facial edema, and red eyes). Oculorespiratory syndrome was first reported in Canada after influenza vaccination during the 2001-2002 influenza. The signs and symptoms of oculorespiratory syndrome include red eyes, cough, wheezing, and chest tightness. Oculorespiratory syndrome presents in the first 24 hours post-vaccination and is typically mild and self-limited. [“Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2011,” MMWR 2011 August 26; 60 (33):1128-1132.]

Immunogenicity: Results for the primary immunogenicity endpoints are shown in the following table. The results were provided for assay results using both egg- and cell-based antigens in the HAI assay.

Reviewer comment: The study was conducted in 2005-2006 and was affected by the pipetting issues described in Section 4.2 of this review. However, this was the only study in which the HAI assays were repeated using both egg- and cell-derived antigens. The results provided are those for the HAI assays after correction of the pipetting issues.

Table 60: Non-Inferiority Comparison of Flucelvax to Fluvirin Based on Day 22 GMT Ratios

Influenza Strain	Day 22 GMT	Day 22 GMT	GMT Ratio (95% CI)*
	Flucelvax N=307	Fluvirin N=303	Flucelvax/Fluvirin
Egg-derived			
A/H1N1	259	306	0.85 (0.70)
A/H3N2	181	320	0.57 (0.46)
B	179	157	1.14 (0.95)
Cell-derived			
A/H1N1	468	508	0.92 (0.76)
A/H3N2	287	468	0.61 (0.503)
B	176	134	1.31 (1.09)

*LL 95% CI = lower limit 95% confidence interval

Source: BLA 125408/0, CSR for V58P5, Tables 11.4.1.1-1, page 60

As shown in the table, protocol-specified non-inferiority criteria were met for all of the endpoints except for the antibody response to influenza A/H3N2 in the HAI assay using egg-derived antigens. The applicant attributes the lower antibody response to A/H3N2 in the Flucelvax arm to the lower geometric mean titer at baseline in the Flucelvax arm (10 in egg-derived antigen assay and 16 in cell-derived antigen assay) compared to the Fluvirin arm (13 in egg-derived antigen assay and 21 in cell-derived antigen assay).

Reviewer comment: The HAI GMT results were similar regardless of antigen used in the HAI assay. All three criteria for demonstration of the non-inferiority of Flucelvax to Fluvirin were met using the cell-based antigens. The results met two of the three criteria for demonstration of the non-inferiority of Flucelvax to Fluvirin using egg-based antigens. Non-inferiority was not demonstrated for the antibody response to influenza A/H3N2 strain, which the applicant attributes to lower GMTs in the Flucelvax arm at baseline. In the opinion of this reviewer, the differences in GMT at baseline were small and were not likely to have resulted in substantially lower antibody titers; however, the results for this endpoint were only slightly lower (0.4) than required for demonstration of non-inferiority.

Safety: The percentage of subjects with any solicited adverse reaction was 79% in the Flucelvax arm and 80% in the Fluvirin arm. Induration was the only local solicited adverse reaction reported more frequently in the Flucelvax arm (9%) than in the Fluvirin arm (6%); malaise was the only systemic solicited adverse reaction reported more frequently in the Flucelvax arm (25%) than in the Fluvirin arm (24%).

Reviewer comment: The overall percentage of subjects with solicited adverse reactions was lower in the Flucelvax arm compared to the Fluvirin arm. Of the five individual solicited adverse reactions, which were reported more frequently in the Flucelvax arm, the differences in rates between the two study arms were small. There was no evidence of oculorespiratory disease.

The percentage of subject with unsolicited adverse events in the seven days post-vaccination was 16% in the Flucelvax arm and 25% in the Fluvirin arm. The most frequently reported unsolicited AE in both arms was pharyngolaryngeal pain. There were no deaths. There were eight serious AEs reported: three in the Flucelvax arm and five in the Fluvirin arm. None of the SAEs were reported within 30 days of vaccination and none were judged as related to study vaccine.

Reviewer comment: On review of the adverse event dataset, no AEs of hypersensitivity, urticaria, or rash were noted in the Flucelvax arm. In addition, there were no AEs of Guillain Barré syndrome or of oculorespiratory syndrome. Overall, the rates and types of adverse events were similar in the two vaccine arms.

6.6 Study V58P14

The applicant briefly described Study V58P14 in the risk management plan section of the BLA. Study V58P14 was a Phase 4, randomized, observer-blind, active-control study to evaluate the safety and immunogenicity of Flucelvax or Agriflu in adults with and without underlying medical conditions. The study was conducted as a postmarketing commitment following the licensure of Flucelvax (Optafu) in Europe. The study was discontinued prematurely due to production issues with Flucelvax, which lead to the lack of available Flucelvax for use in the study. In addition, the applicant states that there were Good Clinical Practice violations noted in this study. The study will not be completed.

At the time of study termination, 1001 subjects had received Flucelvax and 396 had received Agriflu. Serious adverse events were reported in 2.0% of subjects who received Flucelvax and in 2.5% who received Agriflu. Only one SAE was reported within one week of vaccination: herpes zoster was reported two days after vaccination with Flucelvax. There were no reports of anaphylaxis or hypersensitivity that were temporally related to vaccination with either study vaccine.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

The single indication for this product is: For active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. Flucelvax is approved for use in persons 18 years of age and older.

Results of three Phase 3 studies were included in this application. The main support for efficacy was Study V58P13, a clinical endpoint study in 11,299 subjects with 3,818 exposed to Flucelvax. A second study (V58P4) provided support for immunogenicity and safety in the elderly (65 years of age and older). There were substantial concerns about the conduct of the third study (V58P9),

and, in the opinion of this reviewer, the results of this study cannot be used to support the safety, immunogenicity, or lot consistency of Flucelvax.

Because the efficacy endpoint of V58P13 was the percentage of subjects with virus culture-positive influenza illness and the immunogenicity endpoints of V58P4 were antibody responses to vaccination, the primary results of the two studies cannot be combined. Please see Section 6.0 for discussions of the results of both studies.

7.1.1 Persistence of Efficacy

Vaccination against seasonal influenza is recommended yearly because of frequent changes in circulating influenza strains. See “Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2011,” MMWR 2011 August 26; 60 (33):1128-1132. The clinical endpoint study, V58P13, was conducted over an entire influenza season, and the results are appropriate for the recommendation for yearly vaccination.

7.1.2 Product-Product Interactions

In the studies of Flucelvax included in this application, Flucelvax was administered alone with concomitant administration of other vaccines forbidden by the study protocols. The proposed package insert states that “There are no data to assess the concomitant administration of Flucelvax with other vaccines.”

7.1.3 Efficacy Conclusions

The efficacy of Flucelvax is supported by the results of a clinical endpoint study (V58P13). Please see Section 6.1 for a full discussion of the results of this study. In this study, the primary objective was to compare the prevention of illness due to culture-confirmed influenza strains antigenically similar to those contained in the study vaccine after vaccination with Flucelvax or placebo. Vaccine efficacy would be demonstrated if the lower-bound one-sided 97.5% confidence interval for vaccine efficacy was greater than 40%. As shown in the following table, vaccine efficacy was demonstrated by Flucelvax.

Table 61: Study V58P13 - Point Estimate and One-Sided 97.5% Confidence Interval (CI) for Vaccine Efficacy against Vaccine Matched Influenza Strains (Per Protocol Efficacy Population)

	Total # subjects	# Subjects with Influenza	Attack Rate	Vaccine Efficacy (vs. Placebo)	97.5% CI*
Flucelvax	3776	7	0.19%	83.8%	61.0
Placebo	3843	44	1.14%	--	--

Source: BLA 125408/0, CSR for V58P13, Table 11.4.1.1.1-1, page 73

The majority of vaccine matched influenza strains were influenza A/H1N1. Therefore, efficacy against vaccine matched strains was due to efficacy results against influenza A/H1N1 subtype. However, Flucelvax showed effectiveness against mismatched strains of influenza A/H3N2

(point estimate of 75.6%) and influenza B (point estimate of 49.9%). When all influenza isolates were considered (e.g. vaccine matched and vaccine mis-matched strains), the point estimate for vaccine efficacy was 58.7% and the lower limit of the one-sided 97.5% confidence interval was 33.5%.

The effectiveness of Flucelvax in elderly subjects, 65 years of age and older, was established in the results of Study V58P4, comparing HAI antibody responses after Flucelvax to HAI antibody responses after Agriflu, as are described in Section 6.2 of this review. In Study V58P4, elderly was defined as 61 years of age and older. A post-hoc analysis was performed to examine the results for subjects 65 years of age and older. The criteria for demonstration of non-inferiority were that the lower limit of the 95% confidence interval for the difference in seroconversion rate and for the difference in the percentage of subjects with post-vaccination HAI titers $\geq 1:40$ was $> -10\%$, and that the upper bound of the two-sided confidence interval on the ratio of the GMTs ≤ 1.5 . The results are shown in the following table.

Table 62: Study V58P4 - Non-inferiority Analysis of FLUCELVAX to a US licensed Comparator (Agriflu) in Adults 65 Years of Age and Older (Study 2*)

	Vaccine Group Ratio/Difference (95% CI) Flucelvax Versus Agriflu		
	A/H1N1	A/H3N2	B
GMTs ratio (Flucelvax / Agriflu)	1.06 (0.92, 1.22)	0.97 (0.84, 1.12)	1.28 (1.1, 1.48)
Difference in Seroconversion Rates (Flucevax – Agriflu)	-1% (-7, 6)	3% (-2, 9)	7% (1, 12)

Source: BLA 125408/0, Section 1.14.1.2

In conclusion, the vaccine efficacy of Flucelvax against culture-positive influenza disease due to both vaccine-matched and all (matched and mis-matched) influenza strains was demonstrated in a large, placebo controlled trial of subjects from 18 to 49 years of age. Vaccine efficacy in adults, 18 years of age and above, including in a subgroup of elderly subjects, was established in a second trial in which the antibody response after Flucelvax was non-inferior to that of a US-licensed vaccine. Overall, these results support the efficacy of Flucelvax in individuals 18 years of age and above.

8. INTEGRATED OVERVIEW OF SAFETY

A total of 6138 adults from 18 to 64 years of age and 572 subjects 65 years of age and older received Flucelvax in the studies submitted in this BLA.

Of note, safety results were presented in the individual safety reports for subjects 18 to 60 years and for subjects 61 years and older. The reanalysis by age groups 18 to 64 and 65 years and older was performed in the ISS only, which resulted in safety results in the ISS that are difficult to verify or reconcile with individual Clinical Study Reports.

8.1 Safety Assessment Methods

All subjects were followed for local and systemic reactogenicity for seven days post-vaccination. All unsolicited adverse events were followed for 21 days in the majority of subjects. Although the follow-up for serious adverse events and for adverse events leading to premature study discontinuation was only 21 days in two of the Phase 1/2 studies, follow-up was 180 days in the Phase 3 studies. In the opinion of this reviewer, the size of the safety database and follow-up were sufficient to assess the safety of an unadjuvanted, trivalent influenza vaccine.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The studies used in this reviewer's integrated summary of safety were V58P13, V58P4, V58P1, V58P2, and V58P5. Because of concerns with the study conduct in Study V58P9, the safety results from that study are included in descriptions of pooled solicited adverse reactions and common adverse events only. In addition, only some of the safety results from V58P4E1 are included in this summary of safety since this was a re-vaccination study. The percentage of subjects with solicited adverse reactions may have differed on repeated exposure to Flucelvax; therefore, comparison of the results of a re-vaccination study and a study with the first exposure to Flucelvax would not be appropriate in this analysis. The source of each analysis will be identified to allow identification of studies included.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

In the seven studies included in the BLA, a total of 6,710 subjects were exposed to a single, 0.5 mL, intramuscular dose of Flucelvax. This is the dose and the method of administration that will be described in the package insert. In the 18 to 64 year old age group, the mean age of subjects was 34.6 years, 56% of subjects were female, and 90% were Caucasian. In the 65 years and older age group, the mean age was 71.3 years, 55% of subjects were female, and 100% were Caucasians. The percentage of non-Caucasians included in this BLA was small; however, there is no known association of antibody response to or safety of influenza vaccine by gender or race; therefore, the study population should reflect the immune response and safety of Flucelvax in the U.S. population.

8.2.3 Categorization of Adverse Events

Adverse events were reported in the Clinical Study Reports as Preferred Terms using the MedDRA dictionary. The actual term used by the investigator for the adverse event was provided in the datasets.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Information on unsolicited adverse events was collected for 21 days post-vaccination in four of the five studies but only for 7 days post-vaccination in the large, Phase 3 clinical endpoint study. Information on serious adverse events, deaths, and adverse events leading to premature study discontinuation were collected for the entire study period, which was 180 days post-vaccination in three studies and 21 days post-vaccination in two studies. As a result, the safety data from the studies can be pooled for these events. Although the percentage of subjects with unsolicited adverse events including SAEs may be lower in two of the studies and result in an underestimation of total percentage of SAEs, it is relatively unlikely that unsolicited adverse events with an onset more than 21 days post-vaccination were vaccine-related.

8.4 Safety Results

8.4.1 Deaths

There were seven deaths in subjects who received Flucelvax in the seven clinical studies included in this integrated safety summary. In the same studies, there were five deaths in the active influenza control arms and one in the placebo arm. A summary of the deaths are shown in the following table.

Table 63: Subject Deaths in Clinical Studies of Flucelvax

Subject Number	Vaccine	Age (yrs)	Cause of Death	Study Day
09281	Flucelvax	35	Dyspnea	153
35169	Flucelvax	38	Unknown	75
010128	Flucelvax	57	Suicide by drug ingestion	?*
09281	Flucelvax	58	Suffocation due to neck compression	50
032147	Flucelvax	73	Carbon monoxide poisoning	25
012152	Flucelvax	74	Acute myocardial infarction	61
052148	Flucelvax	88	Sudden cardiac death	35
17299	Agriflu	37	Homicide	99
012259	Agriflu	75	Hypertension/CVA	43
042009	Agriflu	77	Adenocarcinoma of lung	189
012221	Agriflu	77	Acute pancreatitis/peritonitis	120
012554	Agriflu	77	Cerebral hemorrhage	134
31320	Placebo	31	Cerebral hemorrhage	33

*Exact date of suicide unknown but occurred within one month of study vaccination.

Source: BLA 125408/0, ISS, Table 2.1.2-1, page 67

None of the deaths were judged by the investigator as vaccine-related. Two deaths were reported within 30 days of vaccination; one death was due to carbon monoxide poisoning in a 73 year old, who was helping with a neighborhood house fire and the other death was due to suicide. There were three deaths in subjects, who received Flucelvax and who were younger than 65 years of age. One of these was due to suicide; the other two were both subjects in Study V58P13: Subject 09281 was a 35 year old Black female with a history of obesity and hypertension who received Flucelvax in Study V58P13. She developed trouble breathing approximately five months post-vaccination and was admitted to the hospital. During the hospitalization, she suffered respiratory arrest, and resuscitation efforts failed. She died on Day 153; death was attributed to obesity (weight of approximately 400 lbs). Subject 35169, a 38 year old Caucasian male with a history of hypertension, depression, and alcoholism; and of hypoglycemia, hypokalemia, and hyponatremia with no known etiology. He was found dead on Day 75; the death was presumed to be due to his one of his medical conditions. No autopsy report is available for this subject.

The number of deaths was the same in the Flucelvax arms and in the control arms. There was no increase in deaths due to adverse events in a single system organ class and no increase in any individual adverse event leading to deaths. The majority of deaths occurred more than one month after vaccination with Flucelvax. In the opinion of this reviewer, none of the deaths were related to study vaccination.

8.4.2 Nonfatal Serious Adverse Events

In the 18 to 64 year cohort, there were 104 serious adverse events reported in Flucelvax recipients, 62 in active control recipients, and 42 in placebo recipients. The percentage of subjects in this age cohort with SAEs was 1% in each arm. The only SAEs reported in more than two subjects in any arm in this age group (as listed in ISS Table 2.7.4.2.3) were:

- Hypertension, which was reported in three Flucelvax recipients,
- Pneumonia, which was reported in one Flucelvax recipient and three active control recipients, and
- Influenza, which was reported in six Flucelvax recipients and four active control recipients

In this age group, 14 subjects experienced SAEs within 30 days of vaccination with Flucelvax, 11 subjects had SAEs within 30 days of receiving the active control, and 5 had SAEs within 30 days of receiving placebo. Thirteen subjects had SAEs within three weeks of receiving Flucelvax; the only SAE reported in more than one Flucelvax recipient during the three weeks post-vaccination was chest pain. Eleven subjects in the active control arm experienced SAEs within three weeks of vaccination; no individual SAE was reported in more than one subject. SAEs were reported in five placebo subjects within three weeks of vaccination, and the only SAE reported in more than one subject was pharyngitis. SAEs reported within seven days of study vaccination were acute MI, ankle fracture, and joint contracture in the Flucelvax arm; appendicitis in the active control arm, and two SAEs of pharyngitis in the placebo arm.

In the elderly (65 years and older) cohort, 50 SAEs were reported in subjects who received Flucelvax and 54 in subjects who received the active control. The percentage of subjects with SAEs was 4% in both the Flucelvax arms active control arms. Serious adverse events reported more than twice in either study arm (Flucelvax or active control) were:

- Acute myocardial infarction, which was reported in three subjects in the Flucelvax arm and one in the active control arm,
- Angina, which was reported in four subjects in the active control arm and none in the Flucelvax arm,
- Atrial fibrillation, which was reported in four subjects in the Flucelvax arm and three in the active control arm, and
- Cholelithiasis, which was reported in three subjects in the active control arm and none in the Flucelvax arm.

The majority of serious adverse events (10 in each arm) was reported in cardiovascular system and was common diseases reported in the elderly, such as myocardial infarction, arrhythmias, and hypertension. There was no single preferred term that was reported at an increased rate in the cardiovascular class or other organ classes. Four elderly subjects in each arm experienced SAEs within 30 days of vaccination. None of the SAEs were reported in more than one subject in either arm. Only one subject reported a SAE within one week of vaccination: a subject with atrial fibrillation six days after receiving Flucelvax. Overall, the number and types of SAEs were similar in the Flucelvax arm and the active control arm.

None of the serious adverse events in the studies included in the application were considered vaccine related.

8.4.3 Study Dropouts/Discontinuations

Seventeen subjects withdrew from a study prematurely due to adverse events. This includes the 13 deaths described in Section 8.4.1 and four additional subjects. Three subjects who received Flucelvax discontinued a study prematurely:

- Subject 21369 was a 39 year old White male whom the investigator removed from the study after the subject had a skull fracture with extradural and subdural hematomas requiring surgery on Day 73 after vaccination with Flucelvax.
- Subject 010322 was a 71 year old White male who withdrew from the study on Day 18 due to syncope. Syncope was attributed to a pre-existing arrhythmia.
- Subject 012152 was a 73 year old White male in the Flucelvax arm who withdrew on Day 54 after an acute myocardial infarction.
- Subject 012477 was a 74 year old White female in the active control arm who withdrew from the study on Day 63 due to an acute myocardial infarction.

None of these adverse events were temporally related to the study vaccine. There was no single and/or unexpected adverse event leading to study discontinuation.

8.4.4 Common Adverse Events

Adverse events that were observed in more than 10% of adult subjects who received Flucelvax were injection site pain, injection site erythema, headache, fatigue, myalgia, and malaise. Adverse events reported in more than 10% of elderly subjects (≥ 65 years) were injection site erythema, fatigue, headache, and malaise.

The percentage of adult subjects from 18 to 64 years of age who reported an unsolicited adverse event in the seven days post-vaccination ranged from 5 to 9% in the Flucelvax arms, from 3 to 23% in the active control arms, and was 10% in the placebo arm. Information on unsolicited AEs was not collected in Studies V58P5 or V58P13 after the first seven days. The percentage of adult subjects reporting unsolicited AEs for the 21 days post-vaccination ranged from 9 to 23% in the Flucelvax arms of the other studies and from 7 to 31% in the control arms. The most frequently reported unsolicited AEs were common illnesses reported in adults such as oropharyngeal pain, cough, headache, malaise and rhinitis. In the analysis of all studies combined, no single unsolicited AEs was reported in more than 1% of subjects in either the Flucelvax or control arm.

In subjects 65 years of age and older, the percentage of subjects reporting unsolicited AEs in the seven days post-vaccination ranged from 4 to 11% in the Flucelvax arms and from 3 to 13% in the control vaccine arms. The percentage of subjects reporting unsolicited AEs in the 21 days post-vaccination ranged from 8 to 21% in the Flucelvax arms and from 6 to 25% in the control vaccine arms. The most commonly reported unsolicited AEs in elderly subjects were malaise, rhinitis, cough, and vertigo. There was no individual AE that was observed in more than 1% of subjects in either the combined Flucelvax or control vaccine arms.

8.4.5 Clinical Laboratory Test Results

Clinical safety laboratory monitoring was performed in two studies: V58P1 and V58P5. However, blood for laboratory testing was obtained on Days 1 and 21 in Study V58P1, therefore, any changes in laboratory results may have been missed e.g., may have resolved by the time of the second blood draw. This review will focus on the results from Study V58P5; in this study, a subset of 120 subjects had blood for laboratory monitoring collected on Day 1, prior to vaccination, and on Day 8. The safety laboratory tests performed were a complete blood count

with differential and platelet count, ALT, AST, bilirubin, LDH, alkaline phosphatase, electrolytes, BUN, creatinine, and total protein. On analysis of the V58P5 dataset for abnormal laboratory values, there were 60 abnormal laboratory values in 41 subjects in the Flucelvax arm and 70 abnormal laboratory values in 43 subjects in the Fluvirin arm. The most frequently reported abnormal laboratory values on Day 8 in the Flucelvax arm were increased glucose (14 subjects), decreased eosinophil counts (11), and decreased monocyte counts (8). The most frequently reported abnormal laboratory values on Day 8 in the Fluvirin arm were decreased eosinophil counts (21 subjects), decreased monocyte counts (8), and increased glucose (8). Of note, there was one subject in the Flucelvax arm with an increased ALT on Day 8 and one with an increased bilirubin on Day 8; however, both subjects had increased values at baseline.

Reviewer comment: The percentages of subjects with abnormal laboratory values were similar in the two study arms, and there were no safety signals observed in the analysis of safety laboratory values post-vaccination.

There were no clinically relevant changes in vital signs. ECGs were not obtained in any of the clinical studies.

8.4.6 and 8.4.7 Systemic and Local Solicited Adverse Reactions

Approximately one-half of adult subjects who received Flucelvax reported a solicited adverse reaction in the seven days post-vaccination. The most frequently reported local solicited adverse reactions were injection site pain (27% of subjects who received Flucelvax) and erythema (14%); the most frequently reported systemic solicited adverse reactions were headache (16%), fatigue (12%), myalgia (11%), and malaise (10%). The overwhelming majority of these adverse reactions was mild and had resolved by Day 7.

Thirty-five percent of elderly subjects (≥ 65 years) who received Flucelvax reported a solicited adverse reaction. This included 10% with erythema at the injection site and 8% with pain at the injection site. The most frequently reported systemic solicited adverse reactions were fatigue (11%), headache (10%), and malaise (10%). Severe solicited adverse reactions were uncommon and were reported in 1% or fewer of subjects for each of the individual adverse reactions.

8.4.8 Adverse Events of Special Interest

There was a single subject with a hypersensitivity reaction after vaccination with Flucelvax. The subject experienced hoarseness post-vaccination and required treatment with antihistamines but not hospitalization. A second subject reported erythema multiforme on Day 7 post-vaccination, which also required treatment with antihistamines but not hospitalization. Both of these adverse events resolved without sequelae. No AEs of hypersensitivity reaction or allergic reaction to the comparator vaccines were reported. There was no increase in the percentages of subjects with urticaria in subjects who received Flucelvax compared to US-licensed comparators and to placebo. Hypersensitivity is known to occur after vaccination with multiple types of vaccines including influenza vaccines [“Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2011,” MMWR 2011 August 26; 60 (33):1128-1132.] Erythema multiforme has also been reported after influenza vaccine (Samad et al, Erythema multiforme secondary to H1N1 vaccine. Southern Medical Journal. Vol 104 (1):73-74, 2011). While both of these AEs may have been related to an allergic type of reaction to Flucelvax, other evidence of allergic reactions to Flucelvax, such as urticaria, rash, and flushing were uncommon and were observed in similar percentages in the

control arms. In the opinion of this reviewer, there does not appear to be an increased risk of serious allergic reactions following vaccination with Flucelvax.

8.5.1 Dose Dependency for Adverse Events

The only dose studied in the five studies of this application was 0.5 mL dose with 15 µg of each of the three influenza antigens recommended for the influenza season studied. All doses of Flucelvax were administered intramuscularly in the deltoid muscle.

8.5.2 Time Dependency for Adverse Events

The majority of adverse events post-vaccination were captured in the week post-vaccination as solicited adverse reactions, which are discussed in Sections 8.4.6 and 8.4.7 of this review. No other adverse events had a temporal relationship to study vaccination.

8.5.3 Product-Demographic Interactions

Safety results for all studies were analyzed by age, gender, and ethnicity by the applicant. The safety profile differed by age with fewer solicited adverse events reported in elderly subjects. Any solicited adverse reaction was reported by 51% of adult subjects from 18 to 64 years of age and by 35% of elderly subjects 65 years of age and older. The percentage of subjects with individual local solicited adverse reactions was higher in subjects 18 to 64 years of age compared to subjects 65 years of age and older with the exception of ecchymosis, which was reported in 4% of subjects in each age groups. Individual systemic solicited adverse reactions were reported in either the same or fewer percentage of elderly as adult subjects for all reactions except fatigue (reported in 13% of elderly and in 11% of younger adults) and arthralgia (reported in 7% of elderly and 4% of younger adults). The lower rate of solicited adverse reactions in elderly subjects has been observed in other vaccine trials and may be due to immunosenescence.

In the analysis of safety by gender, the percentage of adult subjects with any solicited adverse reaction was slightly higher in females (57%) than in males (42%). This was due to the increased percentage of females with local solicited adverse reactions (41% compared to 30% in males) and in systemic adverse reactions (34% of females and 23% of males); these differences were also observed in the control arms. There was an increase in the percentage of female subjects with each individual local solicited adverse reaction compared to males. The only individual solicited adverse reaction observed at a statistically significant higher percentage of females than males was induration at the injection site (risk ratio of 1.20). The rate of subjects with severe adverse reactions was low and was similar in females and males. A higher percentage of females with solicited adverse reactions was also reported in elderly subjects.

The overwhelming majority of adult subjects (90%) who received Flucelvax in studies in this application were Caucasian; therefore, it is difficult to reach any conclusions about safety in non-Caucasians. According to the applicant, there was a statistically significant increase in the percentage of adult subjects reporting pain at the injection site in Caucasians (27%) compared to non-Caucasians (23%). All elderly subjects were Caucasian.

Overall, there were no safety concerns associated with any demographic subgroup.

8.5.4 Product-Disease Interactions

Not applicable

8.5.5 Product-Product Interactions

Not applicable

8.5.6 Human Carcinogenicity

Flucelvax has not been evaluated for carcinogenic or mutagenic potential.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There is no potential for drug abuse, withdrawal, or rebound.

8.5.8 Immunogenicity (Safety)

There are no safety concerns that correlate with antibody response.

8.5.9 Person-to-Person Transmission, Shedding

Flucelvax is an inactivated, subunit influenza vaccine; therefore, there is no shedding of influenza virus post-vaccination.

8.6 Safety Conclusions

The most frequently observed adverse events after vaccination with Flucelvax were adverse reactions in the seven days post-vaccination. Pain at the injection site and injection site erythema were reported in more than 10% of subjects 18 to 64 years of age who received Flucelvax. Erythema at the injection site was reported in more than 10% of subjects 65 years of age and older. Headache, fatigue, and myalgia in the week after vaccination were also relatively common and were reported in more than 10% of subjects who received Flucelvax. These results were similar in the control arm (Agriflu) and are generally comparable to the data from other inactivated seasonal influenza vaccines.

There were no differences between the percentage of subjects with deaths, serious adverse events, or unsolicited adverse events between the groups of subjects who received Flucelvax and groups that received an active comparator. There was no increase in any individual adverse event or class of adverse events in Flucelvax recipients. Overall, no safety signals were identified by this reviewer.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

The applicant has conducted a preclinical reproductive and developmental toxicity study of Flucelvax. (Please see the toxicology review of this application). There was no increased risk to the fetus in the animal model studied. No clinical trials have been conducted in pregnant women. Therefore, Flucelvax will be labeled as pregnancy category B.

Reviewer comment: Pregnancy category B is used for vaccines for which there is an absence of adequate human studies and no fetal risk is observed in animal studies.

All of the currently approved trivalent inactivated influenza vaccines are pregnancy category B or C.

A total of 60 women became pregnant during safety follow-up of the studies in this application. This included 18 in the Flucelvax arms, 24 in the Agriflu or Fluvirin arms, and 18 in the placebo arm. The outcomes of the pregnancies are shown in the following table.

Table 64: Pregnancy Outcomes in Trials of Flucelvax

	Flucelvax N=18	Agriflu/Fluvirin N=24	Placebo N=18
Healthy newborn without congenital anomalies	12	17	13
Spontaneous abortion	2	2	1
Ectopic pregnancy	1	1	0
Unknown outcome (Lost to follow-up)	3	4	4

Source: BLA 125408/0, ISS, Text, Section 5.4, page 113

None of the studies were designed to study the use of Flucelvax during pregnancy and all study protocols excluded enrollment of pregnant women. Only 18 pregnancies were reported in women who received Flucelvax. In the opinion of this reviewer, the data are not adequate to reach any conclusions about the safety of Flucelvax during pregnancy.

9.1.2 Use During Lactation

Flucelvax has not been evaluated in nursing mothers. It is not known if Flucelvax is excreted in human milk.

9.1.3 Pediatric Use and PREA Considerations

The application contains the results of a single study in pediatric patients, Study V58P12. This was a safety and immunogenicity study in which approximately 2200 pediatric patients from 3 to 17 years of age administered Flucelvax. The applicant was informed in 2010 that the safety database in the pediatric population should include approximately 3,000 exposed children. The applicant is planning three additional pediatric studies:

- Study V58P16 will be an immunogenicity, dose ranging, and safety study in approximately 360 subjects from 6 months to < 4 years of age. Subjects will be stratified by age and randomized to receive a full, half or double dose of Flucelvax (120 subjects per dose). Effectiveness will be assessed by antibody response (seroconversion and post-vaccination antibody titers). The safety results after vaccination with Flucelvax will be compared to those observed after vaccination with the active control, which will be a US-licensed vaccine.
- Study V58_31 will be a safety study in approximately 1066 pediatric subjects 4 to 17 years of age. Study subjects will be randomized 3:1 to Flucelvax or to a US-licensed control. This study is to begin no earlier than fall 2013.
- Study V58_35 will be a safety and immunogenicity study in subjects from 6 months to < 4 years of age. The antibody response to Flucelvax will be compared to that to a US-licensed control using a non-inferiority study design.

The requirement for clinical studies in children 0 to <6 months of age were waived, because available data in infants <6 months of age indicate that serum antibody responses to inactivated influenza vaccines in this age group are not as robust as in older children due to inherent immaturity of the immune system and interference from maternal antibody. Thus, use of

Flucelvax in infants <6 months of age would provide no meaningful therapeutic benefit over initiating vaccination at 6 months of age, and this vaccine is not likely to be used in a substantial number of infants < 6 months of age.

The requirement for clinical studies in children 6 months to < 18 years of age were deferred; because the product is ready for approval in adults, and pediatric studies have not been completed.

The results from Study V58P12 will be reviewed in full at the time of submission of the pediatric efficacy supplemental BLA. Briefly, Study V58P12 was a randomized, controlled, observer-blind, safety and immunogenicity study comparing Flucelvax to Fluvirin in healthy children from 3 to 17 years of age. Subjects were enrolled sequentially into one of three study cohorts: Cohort 1 – 300 subjects from 9 to 17 years of age were to be randomized in a 1:1 ratio to receive Flucelvax or Fluvirin. Serum samples for antibody titers were obtained on Days 0 and 28. Cohort 2 – 600 subjects from 9 to 17 years of age were to be randomized in a 3:1 ratio to receive Flucelvax or Fluvirin. These subjects were followed for safety only. Cohort 3 – 3000 subjects from 3 to 8 years of age were to be randomized in a 2:1 ratio to Flucelvax or Fluvirin. Antibody titers were to be measured in a subset of 660 subjects in each study arm.

Safety was monitored by collection of information on solicited adverse reactions for seven days post-vaccination and on serious adverse events, new onset chronic diseases and adverse events leading to premature study discontinuation for 180 days after the last study vaccination.

The primary endpoint of the study was demonstration of non-inferiority of Flucelvax to Fluvirin by comparison of GMT ratios and seroconversion rates post-vaccination for subjects in Cohort 3.

A total of 305 subjects were enrolled in Cohort 1, 669 in Cohort 2, and 2630 in Cohort 3. On analysis of the primary endpoint, five of the six criteria for demonstration of non-inferiority were met when cell-based antigens were used in the HAI assay. The seroconversion rate was greater than 40% for all three strains in both age groups.

The safety population included 2251 subjects who received at least one dose of Flucelvax: 652 in the 9-17 year age cohort and 1599 in the 3-8 year age cohort. In the 3-8 year age cohort, local solicited adverse reactions were reported in 38% of Flucelvax recipients and in 35% of Fluvirin recipients. In the 9-17 year age cohort, local solicited adverse reactions were reported in 42% of Flucelvax recipients and in 45% of Fluvirin recipients. The most frequently reported local solicited adverse reaction in both age groups was pain. In the 3-8 year age group, 23% of Flucelvax recipients and 26% of Fluvirin recipients reported systemic solicited adverse reactions. The only systemic solicited adverse reactions reported in 10% or more of subjects were headache and fatigue. In the 9-17 year age group, systemic solicited adverse reactions were reported in 29% of Flucelvax recipients and in 30% of Fluvirin recipients. Systemic solicited adverse reactions reported in 10% or more of subjects were headache, fatigue, myalgia, and malaise. Serious adverse events were reported in less than 1% of subjects. SAEs reported with 30 days of vaccination were mononucleosis, contusion, and depression in the Flucelvax arm and chronic bronchitis in the Fluvirin arm.

9.1.4 Immunocompromised Patients

Flucelvax was not studied in immunocompromised patients.

9.1.5 Geriatric Use

Elderly subjects were enrolled in Studies V58P1, V58P2, V58P4, and V58P4E1. These studies were stratified by age to enroll subjects 18 to 60 years and 61 years and older to meet the EMA definition of elderly. However, CBER defines elderly as 65 years of age and older, so the applicant re-analyzed the data from these four studies for subjects 65 years of age and older. In the four studies, 779 subjects received a dose of Flucelvax. All elderly subjects were Caucasian, 54% were female, and 62% had previously received an influenza vaccine. Since the HAI assays were conducted with the poorly calibrated pipettes and the data from V58P1 were not re-analyzed, the immunogenicity results from this study were not included in the summary. The results of Study V58P4E1 were not included since this was a re-vaccination study of V58P4. The immunogenicity results from subjects 65 years and older in Studies V58P2 and V58P4 are shown in the following table.

Table 65: Point Estimate (Lower Bound 95% Confidence Interval) for Immunogenicity Results in Subjects 65 Years of Age and Older in Studies V58P2 and V58P4

	Study V58P2						Study V58P4					
	Flucelvax N=38			Agriflu N=48			Flucelvax N=504			Agriflu N=481		
	H3N2	H1N1	B	H3N2	H1N1	B	H3N2	H1N1	B	H3N2	H1N1	B
SCR (%)	32 (18)	8 (2)	34 (20)	10 (3)	10 (3)	31 (19)	68 (64)	55 (50)	80% (76%)	64 (60)	55 (51)	74 (69)
% ≥ 1:40 Day 22	95 (82)	79 63	39 (24)	92 (80)	71 (56)	38 (24)	97 (95)	86 (83)	90 (87)	98 (96)	85 (82)	90 (87)
GMR	2.49	1.51	2.88	1.56	1.62	2.83	7.08	5.43	12	8.35	5.6	9.18

Source: BLA 125408/0, Integrated Summary of Efficacy, Table 3.2.2-8, page 84

After re-analysis of the immunogenicity results from V58P4, Flucelvax was non-inferior to Agriflu in the elderly. These results are shown in the following table:

Table 66: Non-inferiority Comparison of Flucelvax to Agriflu in Subjects 65 Years of Age and Older in Study V58P4

	A/H3N2	A/H1N1	B
GMT Ratio	0.97 (0.84, 1.12)	1.06 (0.92, 1.22)	1.28 (1.1, 1.48)
Seroconversion Rate	3% (-2, 9)	-1% (-7, 6)	7% (1, 12)

Source: BLA 125408/0, Integrated Summary of Efficacy, Table 3.2.2-9, page 87

Overall, the HAI antibody responses to Flucelvax were non-inferior to those to Agriflu, a U.S. licensed vaccine approved for use in the elderly.

On review of the safety results for subjects 65 years of age and older, there was no appreciable difference in the results in subjects who received Flucelvax and those who received the control vaccine. The most commonly reported adverse events in the Flucelvax and control arms were solicited adverse reactions. Thirty-five percent of elderly subjects (≥ 65 years) who received Flucelvax reported a solicited adverse reaction. The most frequently reported local solicited adverse reaction were erythema at the injection site (10%) and pain at the injection site (8%). The most frequently reported systemic solicited adverse reactions were fatigue (11%), headache (10%), and malaise (10%). The percentage of subjects reporting unsolicited AEs in the 21 days post-vaccination ranged from 8 to 21% in the Flucelvax arms and from 6 to 25% in the control vaccine arms. The percentage of subjects with SAEs was 4% in the Flucelvax arms and in the active control arms. The most commonly reported unsolicited AEs and SAEs in elderly subjects were illnesses that are commonly seen in an elderly population. There were three deaths in elderly subjects who received Flucelvax and four in subjects who received control.

10. CONCLUSIONS

The clinical data submitted in this BLA support the safety and effectiveness of Flucelvax when administered to adults 18 years of age and older. The clinical recommendation for approval of Flucelvax is based on the demonstration of clinical benefit as vaccine efficacy against virus culture-confirmed influenza illness was demonstrated in a randomized, placebo-controlled trial of 11,404 healthy adults from 18 to 49 years of age. Immunogenicity and safety in older adults was demonstrated in four studies enrolling subjects 18 years of age and older. The safety concerns are primarily mild local injection site reactions and headache, malaise, myalgia, and fatigue post-vaccination.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

A comparison of the risks and benefits are shown in the following table and are discussed in text after the table.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> Influenza typically causes annual epidemics during the late fall through the early spring. Severity of disease (rates of hospitalization and death) is worst in the elderly, children younger than 2 years of age, and individuals with medical conditions that place them at increased risk for complications. The number of hospitalizations and deaths due to influenza varies each year. The CDC has reported a range of 3,000 to 49,000 deaths per year in the US due to influenza in the 30 years prior to 2007. 	<ul style="list-style-type: none"> Considerable morbidity and mortality is associated with yearly influenza epidemics. Influenza vaccines are the most effective way of preventing morbidity and mortality due to influenza.
Unmet Medical Need	<p><u>There are currently five trivalent, inactivated vaccines licensed in the U.S. for prevention of seasonal influenza in adults: Fluzone™, Fluvirin™, Fluarix™, Afluria™, FluLaval™, and Agriflu™. All of these vaccines are produced in embryonated hen eggs. There is also a live attenuated trivalent vaccine, FluMist, licensed in the U.S. This virus is attenuated by multiple passages in eggs.</u></p> <ul style="list-style-type: none"> The use of eggs in the manufacture of these influenza vaccines results in a reliance on egg supply, long production timelines, difficulty with scaling up production in an emergency, and the inclusion of egg proteins in the vaccines. 	<ul style="list-style-type: none"> Flucelvax would be the first cell derived influenza vaccine licensed in the U.S. Since Flucelvax is manufactured in MDCK cells instead of eggs, the manufacturing will not be dependent on eggs and production scale up may be quicker. Flucelvax contains almost unmeasurable amounts of egg proteins and may be the first influenza vaccine appropriate for use in persons with egg allergy. However, Flucelvax has not been studied in subjects with egg allergies.
Clinical Benefit	<ul style="list-style-type: none"> Vaccine efficacy was demonstrated in a randomized, placebo-controlled trial of 11,404 healthy adults from 18 to 49 years of age. Vaccine efficacy against vaccine-matched influenza strains was 83.8% and against all strains (matched and mis-matched) was 69.5%. 	<ul style="list-style-type: none"> Clear evidence of clinical benefit was demonstrated in a large, appropriately designed trial.
Risk	<ul style="list-style-type: none"> The most commonly reported adverse events associated with Flucelvax were pain and erythema at the injection site and headache, fatigue, malaise, and myalgia. There was one report of hypersensitivity and one of erythema multiforme after vaccination with Flucelvax. 	<ul style="list-style-type: none"> The most common safety risks are relatively minor adverse reactions that were typically mild and resolved in several days after vaccination. The adverse events of hypersensitivity and erythema multiforme were treated with antihistamines and did not require hospitalization. These types of allergic events are observed with all vaccines and the report of only 2 allergic type of AEs does not represent an increased risk over other approved vaccines. The applicant did not provide credible clinical evidence of lot consistency.
Risk Management	<ul style="list-style-type: none"> The most frequently reported risks of vaccination with Flucelvax were reactions at the injection site that were typically mild and resolved within days. These will be described in the package insert Lot consistency was demonstrated by biochemical analysis of consecutive lots of Flucelvax. 	<ul style="list-style-type: none"> The package insert will reflect the safety findings reported in the studies of Flucelvax.

11.2 Risk-Benefit Summary and Assessment

The data submitted in this application support the clinical efficacy of Flucelvax against both influenza strains matched to those in the vaccine, and protection against mismatched vaccine strains was also demonstrated. In addition, Flucelvax would be the first cell-derived influenza vaccine licensed in the U.S.

The use of cell cultures to manufacture Flucelvax may also result in an ability to scale up production more quickly than in eggs and to address a change in antigens due to an unexpected circulating strain more quickly. Finally, the manufacture of Flucelvax will not be dependent on an egg supply. As a result, Flucelvax may be available more quickly or in greater amounts when an unexpected influenza strain circulates or at the time of a egg or vaccine shortage.

The most common risk associated with Flucelvax is pain and erythema at the injection site and headache, malaise, myalgia, and fatigue in the week after vaccination. These adverse events are typically mild and resolve within days. There was one AE of severe hypersensitivity and one of erythema multiforme after vaccination with Flucelvax, but both cases responded to treatment and neither subject was hospitalized. The risk of an allergic reaction is observed with multiple vaccines, including the influenza vaccines already licensed for use in the U.S. Therefore, the risk of an allergic reaction to Flucelvax is low and does not appear to be any greater than with other influenza vaccines.

Due to previously discussed problems with the conduct of the relevant study, clinical lot consistency was not demonstrated for this vaccine. However, consistency of manufacture of multiple lots was demonstrated using physico-chemical and biological tests of final products. In addition, the demonstration of clinical lot consistency is not required in the Code of Federal Regulations and is described as optional in the FDA Guidance for Industry, Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines.” Overall, consistency of manufacture has been demonstrated adequately to support approval. The applicant is establishing a new manufacturing site in the United States and has agreed to conduct a clinical study to demonstrate lot consistency using material produced at that site to provide further data to demonstrate that Flucelvax is being manufactured in a consistent manner.

In the opinion of this clinical reviewer, the benefits of prevention of influenza disease, providing influenza vaccine for egg allergic subjects, and possibly avoiding vaccine shortages (since not dependent on eggs and since can scale up manufacture more quickly) outweigh the risks of mild adverse events, rare allergic reactions, and the lack of clinical data to confirm lot consistency.

11.3 Discussion of Regulatory Options

In the opinion of this reviewer, the clinical endpoint data support the approval of the BLA. Because of the issues involving the conduct of the clinical lot consistency study, regulatory options for establishing consistency of manufacture were discussed. Since the lots are consistent based on physico-chemical characterization, it was determined that the BLA may be approved without clinical lot consistency data. A clinical lot consistency study will be conducted post-marketing as the applicant moves production of Flucelvax to a new facility in the U.S.

11.4 Recommendations on Regulatory Actions

In the opinion of this reviewer, the clinical efficacy and safety data submitted in this application support the approval of this BLA.

11.5 Labeling Review and Recommendations

Revisions to the package insert were discussed with the applicant. The main issues were:

- the amount of immunogenicity and safety data included in the package insert,
- inclusion of language about the use of Flucelvax in persons with egg allergy,
- the inclusion of adverse events from postmarketing experience with other influenza vaccines, since there are no postmarketing adverse event data available from the doses of Flucelvax that were distributed in Europe.

11.6 Recommendations on Postmarketing Actions

The applicant has agreed to the following postmarketing commitments:

1. Novartis Vaccines and Diagnostics agrees to conduct Study V58_31, a randomized, observer-blind, safety study of Novartis's Flucelvax in a pediatric population from 4 years to 17 years.
2. Novartis Vaccines and Diagnostics agrees to conduct Study V58P16, a randomized, observer-blind, dose-finding, safety, and immunogenicity study of Novartis's Flucelvax in a pediatric population from 6 months to < 4 years of age.
3. Novartis Vaccines and Diagnostics agrees to establish a pregnancy registry to prospectively collect data on spontaneously-reported exposures to Flucelvax during pregnancy.
4. Novartis Vaccines and Diagnostics agrees to conduct a clinical lot consistency study comparing three consecutive lots of Flucelvax manufactured at Novartis's Holly Springs facility.