Title Page and General Information

BLA number: 125127

Related IND numbers: [redacted], and [redacted]

Reviewer Name, Division and Mail Code:

Clinical Reviewer: Joseph G. Toerner, MD, MPH. CBER/OVRR/DVRPA/Clinical Trials Branch, HFM-475 Joseph Toerner Aug 17, 2005
Supervisory Reviewer: Antonia Gèber, MD, Team Leader, HFM-475

Submission Received by FDA: May 27, 2005 Aug 18, 2005

Review Completed: August 17, 2005

PRODUCT

Proper Name: Influenza virus vaccine
Proposed Trade Name: Fluarix
Product Formulation Including Preservatives:

The 2005-2006 vaccine contains HA from three influenza strains (total HA = 45 µg)

A/ New Caledonia/20/99 (H1N1):	15 µg
A/New York/55/2004 (H3N2):	15 µg
B/Jiangsu/10/2003:	15 µg

Fluarix contains the following excipients: sodium chloride, [redacted] alpha-tocopheryl hydrogen succinate, polysorbate 80 (Tween 80), octoxynol 9 (Triton X-100), and water. Fluarix is preservative-free, but contains residual levels of thimerosal from early stages of manufacturing; maximum thimerosal content was 0.0025 mg per dose.

Applicant: GlaxoSmithKline, Inc. (heretofore called "applicant" or "GSK")
Pharmacologic Class or Category: Vaccine
Proposed Indication: Active immunization of adults against influenza disease caused by influenza virus types A and B contained in the vaccine
Proposed Population: Adults 18 years of age or older
Dosage Form and Route of Administration: 45 µg dose, administered intramuscularly, trivalent formulation.

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3 Executive Summary

- The trivalent inactivated influenza vaccine Fluarix should be approved for active immunization of adults against influenza disease caused by influenza virus types A and B contained in the vaccine. The recommendation for accelerated approval of Fluarix by the clinical reviewers is based on the demonstration of efficacy by a surrogate endpoint: the immune response following administration of Fluarix. A randomized, placebo-controlled, double-blinded study showed that subjects randomized to receive Fluarix had immune response criteria that exceeded the pre-defined successful endpoints. While there are no known correlates of immune protection for influenza, these pre-defined immune response criteria have a reasonable likelihood of predicting clinical efficacy. There were no patterns of unusual safety concerns associated with administration of Fluarix. Therefore, the potential benefits of adminstration of Fluarix are well-balanced against the potential risks. With this accelerated approval, the availability of an additional trivalent influenza vaccine provides meaningful benefit in the setting of potential shortages of influenza vaccine. The license application contained safety and immune response data from three other studies, which included 246 adults greater than or equal to 65 years of age. Post-hoc analyses demonstrated acceptable safety characteristics and favorable immune response data in the geriatric population greater than or equal to 65 years of age. The applicant has agreed to conduct a clinical endpoint efficacy study that will confirm the efficacy of the vaccine as supported by the surrogate endpoint of immune response. As well, the applicant will conduct a study to compare immune responses among adults who receive Fluarix versus other trivalent inactivated vaccines licensed in the United States. Finally, the applicant plans to pursue development of Fluarix for use in the pediatric population. Although pediatric studies will be deferred, as defined under Pediatric Research Equity Act the applicant will be required to complete clinical development in the pediatric population with due diligence. Discussions are currently ongoing regarding the development of a thimerosal-free formulation of Fluarix.

4 Significant Findings from Other Review Disciplines

4.1 Chemistry, Manufacturing and Controls (CMC):

- Please refer to the review by Dr. Zhiping Ye.

4.2 Animal Pharmacology/Toxicology:

- The BLA contained a three-page summary of animal toxicology data. The applicant concluded that "Fluarix vaccine was safe when tested on the cardiovascular and respiratory function of the rat and did not induce signs of systemic toxicity when given repeatedly (2 IM injections) to the [redacted] rabbit. Findings were limited to injection sites and consisted mainly of an inflammatory reaction, consistent with a transient response to administration of immunogenic material, and with a tendency to recovery after a 4-week waiting period." The results of animal toxicology studies were not included in the BLA.

5 Clinical and Regulatory Background

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

- Influenza infection is characterized by seasonal epidemics, usually occurring during the winter months in the United States. During the years 1990-1999, influenza infection was responsible for an average of 36,000 deaths per year in the United States. The rates of infection are highest among children, but serious illness and death are reported more frequently among persons greater than or equal to 65 years of age and persons of any age who have chronic underlying medical conditions that place them at increased risk of complications. Influenza vaccination is the primary method for preventing influenza illness and its severe complications. In certain circumstances, antiviral medication can be an important adjunct to the vaccine for prevention and control of influenza.
- The Advisory Committee on Immunization Practices (ACIP) publishes recommendations for groups of persons who should be targeted for routine administration of influenza vaccine, for example, including but not limited to persons greater than or equal to 65 years of age and persons with chronic medical conditions.
- Efficacy and effectiveness of influenza vaccine products have been evaluated in retrospective studies, prospective longitudinal studies, and challenge studies. The range of vaccine efficacy in these studies varies from 22% to 91%. In general, vaccine efficacy appears to be reduced in adults greater than or equal to 65 years of age. In addition, immune response parameters also appear to be reduced in the elderly population.

5.2 Important Information from Pharmacologically Related Products, Including Marketed Products

- Two trivalent inactivated influenza virus vaccines are currently licensed in the United States. Until recently, other vaccine manufacturers produced influenza virus vaccine. Since at least the 1960s influenza vaccines have been available.
- Worldwide surveillance of influenza provides an estimate of the strains of influenza that might be in circulation in the United States. Each year, changes to the antigen content of the vaccine are made based on these surveillance mechanisms so that the vaccine might offer optimal protection from the influenza strains in circulation.

5.3 Previous Human Experience with the Product including Foreign Experience

- The applicant provided immune response and safety data from studies conducted outside the United States in the form of summary tables submitted under IND [redacted] and IND [redacted] Many of these studies were conducted for the purpose of providing safety and immune response data for the yearly antigen changes to the influenza vaccine that is required for registration in European countries. For most years, each immunogenicity parameter of the hemagglutination-inhibition (HI) antibody response met or exceeded the pre-defined criteria established by the Committee for Medicinal Products for Human Use (CHMP) of the European Agency for the Evaluation of Medicinal Products (EMEA). The safety data from these studies were summarized only in the format of solicited adverse events collected on diary cards. Pain, redness, swelling, or induration at the injection site appeared to be the

more commonly reported adverse events. Immune response and safety data from three of these studies were submitted to the BLA for review.

- Summary immunogenicity data and reactogenicity data collected in patients at risk for complications associated with influenza were summarized by the applicant. Six separate studies were conducted between 1995 and 1999 and enrolled patients receiving cancer chemotherapy, solid organ transplant recipients, patients with insulin-dependent diabetes, and patients with chronic obstructive pulmonary disease. The mean ages of study participants ranged from 41.2 to 62.2 years. In general, fewer subjects in these studies reported grade 2 or grade 3 reactogenicity adverse events. Immunogenicity parameters of the HI antibody titer were collected and analyzed in accordance with the recommendations by the CHMP. In all of the studies, each of the three influenza antigens met or exceeded the immunogenicity criteria of the CHMP except for the 1995 study in patients receiving cancer chemotherapy where only 42% achieved a HI antibody titer greater than or equal to 1:40 for the H3N2 antigen.
- Post-marketing surveillance safety data:
- The adverse events collected in clinical trials and collected as part of spontaneous reports were coded using the World Health Organization dictionary for Adverse Reaction Terminology. Of 128,465,524 doses distributed between the years 1996 and 2004, there were 2189 reports of adverse events and 656 reports of serious adverse events according to the applicant.
- From these post-marketing data, the applicant summarized the ten most commonly reported adverse events.

Table 5.1: Common adverse events following administration of Fluarix

Adverse event	Number of events reported	Estimated frequency per 100,000 doses
Pyrexia	658	0.52
Headache	265	0.21
Rigors	232	0.18
Arthralgia	230	0.18
Influenza-like illness	206	0.16
Myalgia	195	0.15
Injection site erythema	169	0.13
Fatigue	145	0.11
Cough	141	0.11
Injection site pain	139	0.11

- The applicant summarized the 38 fatalities following immunization with Fluarix that were spontaneously reported to GSK between the years 1994 and 2004. The majority of the reports were received between the years 1999 and 2004, with one report from 1994 and one

from 1995. The average age of the fatal cases was 70.8 years with a median age of 72 years. The onset of the illness resulting in death averaged 7.1 days following immunization with Fluarix. Seven deaths were related to coronary artery disease. Six deaths were related to complications of infection, some of which were attributed to the possibility of "contaminated" vaccine. Eight deaths were neurological in nature, with four cases of Guillain-Barre syndrome and two cases of encephalitis. A total of 17 fatalities of various causes were reported, from sudden death to pulmonary fibrosis to aortic aneurysm.

- The applicant also submitted a summary of cases of Guillain-Barre syndrome that were reported as non-fatal cases. An additional 43 cases of non-fatal Guillain-Barre syndrome were reported during a time frame when approximately 128 million doses of Fluarix were distributed. An estimated rate is 0.037 cases reported per 100,000 doses distributed. The applicant stated that the background rate of Guillain-Barre syndrome was estimated to be approximately 1-2 cases per 100,000 population.

- The applicant also acknowledged that the enhanced adverse event reports during the 1995-1996 vaccination program in Italy appeared to be associated with their vaccine product Fluarix. The applicant stated: "GSK performed an investigation and modified the manufacturing process to decrease particle size."

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

- On September 17, 2004, GSK submitted a request for a type B pre-IND meeting with the Office of Vaccine Research and Review. The purpose of the pre-IND meeting was to discuss the clinical development of Fluarix that would result in licensure in the U.S. A meeting was scheduled for November 19, 2004, and the sponsor submitted a meeting package on October 22, 2004.

- The U.S. approached the fall of 2004 with two manufacturers of licensed inactivated trivalent influenza vaccine and one manufacturer of live (attenuated), intranasal, cold-adapted trivalent vaccine. Two other influenza vaccine manufacturers had requested a withdrawal of their marketing license over the previous several years. The inactivated trivalent vaccines are recommended by the Centers for Disease Control (CDC) for use in groups of people who are deemed to be at risk for complications of influenza infection. When one vaccine manufacturer experienced product manufacturing problems and the regulatory authorities in the United Kingdom declined to release the influenza vaccine, the U.S. was suddenly faced with a severe shortage of influenza vaccine in October of 2004.

- The CDC began to redistribute available influenza vaccine due to the anticipated shortages within the meaning of Section 503(c)(3)(B)(iv) of the Food, Drug, and Cosmetic Act. The Department of Health and Human Services invited influenza vaccine manufacturers with products approved outside the U.S. to submit proposals for use of their product under an

Investigational New Drug application (IND) in the US. GSK approached the FDA in October of 2004 with a proposal to make Fluarix available to be used under IND status. Therefore, as CDC began to control the distribution of available licensed influenza vaccine, GSK worked in consort with the CDC and FDA in order to provide Fluarix under an IND protocol if sufficient licensed trivalent inactivated influenza vaccine were not available.

- In parallel to these events, FDA held internal meetings to discuss strategies for approving additional vaccines for use in the U.S. for the 2005-2006 influenza season and beyond. FDA also consulted in early November 2004 with the National Institutes of Health (NIH) Division of Microbiology and Infectious Diseases (DMID) to discuss the feasibility of rapidly conducting a reasonably large study through NIH's Vaccine Trials Evaluation Units (VTEU) sites should an industry sponsor wish to avail themselves of these resources. The study would serve as an adequate and well-controlled study that would have a primary endpoint of hemagglutination-inhibition (HI) antibody response to be used as a surrogate endpoint for purposes of accelerated approval. The FDA's Office of Chief Counsel was consulted as to whether recurring influenza vaccine shortages, including the severe shortage experienced in the U.S. during the 2004-2005 season, might fall within the regulatory definitions that would support use of the accelerated approval regulations for the licensure of Fluarix as a new biological product designed to prevent a serious or life threatening illness. The Office of Chief Counsel agreed that the regulatory definition was met based on the CDC's published estimates of an annual need for approximately 185 million doses of influenza vaccine to ensure adequate supply of vaccine to immunize all persons for whom influenza vaccine is recommended.

- CBER and GSK held a pre-IND meeting on November 19, 2004, and representatives from DMID/NIH participated at GSK's invitation. During the meeting, the outline of a trial that might serve as the basis of an accelerated approval was discussed. GSK and NIH agreed to work together in order to conduct and complete a study that would be submitted to CBER for review in support of a BLA for Fluarix. The aim of the applicant and CBER was to conduct the study and complete the study report in a timeframe that would allow for review, and possible approval of the Fluarix vaccine prior to the upcoming 2005/2006 influenza season. While a study that would compare Fluarix to licensed vaccine product might have advantages in this setting of accelerated approval, Fluzone® was not easily available in December 2004 and GSK was unable to obtain Fluzone® for the conduct of a study. A placebo-controlled study that would assess safety and HI antibody response after administration of Fluarix was proposed. A clinical protocol for a randomized, multicenter, placebo-controlled study in healthy adults ages 18-64 years of age in the U.S. was included in the initial IND submission on December 1, 2004, and CBER comments were sent to the sponsor on December 2, 2004. A final protocol incorporating most of the CBER comments was submitted December 8, 2004. Requirements for confirmatory studies to be conducted the following season (2005-2006) to support traditional approval were also outlined by CBER.

ACCELERATED APPROVAL MECHANISM:

The regulations for accelerated approval of a biologic product for serious or life-threatening illness are outlined below:

- 21 CFR 601.40 Subpart E: **Scope**. This subpart applies to certain biological products that have been studied for their safety and effectiveness in treating life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g. ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).

- 21 CFR 601.41: **Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.** FDA may grant marketing approval for a biological product on the basis of adequate and well-controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit on the basis of an endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the biological product further, to verify and describe its clinical benefit, where there is uncertainty of the surrogate endpoint to clinical benefit, or to the observed clinical endpoint to ultimate outcome. Post-marketing studies would usually be already underway. When required to be conducted, such studies must also be adequate and well controlled. The applicant shall carry out any such studies with due diligence.

- In the event of a national shortage of inactivated trivalent influenza vaccine to be used in populations at highest risk of complications and mortality from influenza infection, the regulations might apply to an inactivated trivalent influenza vaccine under BLA review. As the applicant was informed, the regulatory pathway of accelerated approval would be dependent on a well-characterized projected seasonal shortage of inactivated trivalent influenza vaccine at the time of approval.

SURROGATE ENDPOINTS USED IN THE CLINICAL TRIAL:

- The adequate and well-controlled study FluarixUS-001 was conceived, planned, and fully enrolled in less than one month. The study enrollment exceeded the planned minimum numbers, and approximately 950 healthy adult subjects ages 18-65 completed enrollment at four U.S. sites during December of 2004. Subjects were randomized 4:1 to receive Fluarix or saline placebo. Blood was drawn for HI antibody assay at baseline and at approximately three weeks following vaccination. It was anticipated that over 750 subjects who received Fluarix would be available for HI antibody assay titer analyses. The co-primary endpoints were the proportion of subjects with a four-fold or greater rise in HI antibody titers over baseline and the proportion with an HI antibody titer of at least 1:40 at three weeks following vaccination for each of the three vaccine antigens.

- Immunity to influenza involves several components of the immune system and multiple antigens of the influenza virus. The HI antibody assay is a method of evaluating antibody responses to hemagglutinins present on the surface of influenza viruses. The assay conditions and the condition of the cells and viral antigens influence the affinity of the binding that results in visible hemagglutination. Naturally occurring variations in erythrocyte pools from different source flocks and variations originating from the handling of the cells affect the hemagglutination and contribute to the variability between and within laboratories. The HI antibody assay must, therefore, include suitable controls to assure the sensitivity, specificity and uniformity of the assay conditions. The HI antibody assay is generally regarded as a measure of a major component of the protective mechanism.

- Small human challenge studies have evaluated HI antibody titers, and HI antibody titers that appear to be associated with protection from illness, such as HI antibody titers of at least 1:40, have been proposed. However, despite the long history of HI antibody assays used to evaluate immunologic responses to influenza viruses and vaccines, no level of HI antibody titer has been correlated with protection from influenza A or B disease. Hobson and colleagues[1] conducted a meta-analysis of studies designed to evaluate clinical signs and symptoms following inoculation with various influenza virus strains. The studies also collected pre- and post-HI antibody titers that allowed for a correlation between HI antibody titers and degree of infectivity. The results demonstrated a diminished likelihood of infection with increasing HI antibody titer to an influenza B strain, where an estimated titer at which the infection rate reduced to half was 1:18. Similarly, a diminished likelihood of infection with increasing HI antibody titer was demonstrated with an influenza A strain, where an estimated titer at which the infection rate reduced to half was between 1:18 and 1:36. The rates of infection in subjects with no detectable HI antibody appeared to be lower than rates in subjects with low-level detectable HI antibody. Data from field efficacy studies of influenza vaccines have not adequately defined an HI immune response level that correlates with protection. However, these early data have been used to support use of the HI antibody titer in studies in which immune responses to influenza vaccines are being evaluated as well as the use of HI antibody titers by the CHMP of the EMEA, as outlined in table 5.2. Recent studies compared doses and routes of administration of influenza vaccine using the HI antibody assay and demonstrated a reasonably consistent proportion of subjects with a four-fold or greater HI antibody titer or an HI antibody titer of at least 1:40. For example, the study of a full and half strength inactivated influenza vaccine[2] demonstrated point estimates for the full dose that were well above the criteria established by the CHMP.

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[1] Hobson D, Curry RL, Beare AS, Ward-Gardner A. The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. J Hyg 1972;70:767-777.

[2] Treanor J, Keitel W, Belshe R, et al. Evaluation of a single dose of half strength inactivated influenza vaccine in healthy adults. Vaccine 2002;20:1099-1105.

Table 5.2: EMEA immunogenicity criteria for adults, established by CHMP for purposes of yearly registration

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

- In summary, the HI antibody assay has been widely used to measure influenza vaccine activity, and while no specific antibody titer has been demonstrated to correlate with protection, available data suggest that the CHMP criteria might serve as a useful guide for designing a trial to support accelerated approval of a trivalent inactivated influenza vaccine. Specifically, HI antibody titers appear to be reasonably likely to predict clinical benefit, even if one accepts the limitations of a complicated biologic assay with multiple variables that are difficult to control and require careful attention if the test is to provide meaningful results.

- CBER requested a robust statistical analysis plan for study FluarixUS-001 that was based on point estimates with narrow confidence intervals, for example, the lower bound of the 95% CI should not exceed –5%. However, in the original protocol there were no defined criteria for a successful outcome and CBER requested that these criteria be prospectively defined. GSK subsequently submitted a data analysis plan prior to unblinding of the study or analysis of the sera that defined a successful study outcome as having the lower bound of the 95% confidence interval for proportion of subjects with a four-fold increase in HI antibody and proportion of subjects with HI antibody titers ≥1:40 to exceed the CHMP criteria for each of the three antigens (table 5.2 above). Furthermore, the study was adequately powered to meet these six endpoints. In spite of the rapid enrollment, the study was not adequately powered to meet the narrow confidence intervals (95% CI not to exceed –5%) surrounding the anticipated point estimates of proportion with HI antibody titers ≥1:40 and proportion with four fold or greater rise in HI antibody titer. However, CBER viewed the planned statistical analysis of study FluarixUS-001 as acceptable for the following reasons:

  - The lower bounds of the 95% confidence intervals are required to be above the CPMP criteria.
  - All six endpoints are required to be achieved; proportion with HI antibody titers ≥1:40 and proportion with four fold or greater rise in HI antibody titer for each of the three vaccine antigens.
  - The study is adequately powered to meet all of the co-primary endpoints.
  - The endpoints were prospectively defined before unblinding of the subjects and analysis of the sera.
  - A confirmatory clinical endpoint efficacy study will be required as well as immunologic bridging studies to populations for whom the vaccine is universally recommended.

- The use of CHMP criteria introduces some degree of global coordination with other regulatory approval mechanisms for influenza vaccines.

- In addition to study FluarixUS-001, clinical data from other studies would be submitted as part of the license application for the accelerated approval. The complete study report from the original registrational trial that was conducted in 1992 in Europe would be submitted. In addition, the complete study report from a study conducted in Europe in the elderly population would be submitted. In that study, approximately 750 elderly subjects received one of three inactivated influenza vaccine products licensed in Europe; one arm included Fluarix. Therefore, clinical safety and immune response data from additional studies, one of which appeared to be an adequate and well-controlled study, would be reviewed in the license application. The safety data that were collected systematically in clinical studies would be submitted to the BLA for review. The total safety database would consist of approximately 1,271 adults that received Fluarix. The accelerated approval would include the adult population of 18-64 years of age that was represented in study FluarixUS-001. A decision to expand the accelerated approval age range to over age 65 years would depend on FDA review of safety and immune responses in studies where Fluarix was administered to the elderly population.

- The regulations specify that applicants be required to conduct adequate and well-controlled confirmatory studies. The applicant was informed that the accelerated approval mechanism using surrogate endpoints rests upon the commitment to conduct clinical studies to confirm the surrogate endpoint. One recommendation was a placebo-controlled safety and efficacy study with culture confirmed influenza as at least one primary endpoint in a population for whom universal influenza vaccination is not recommended, for example in healthy adults ages 18-49 or 18-64 years. The study should be initiated during the spring in the Southern hemisphere or in the fall in the Northern hemisphere in the year following the accelerated approval. A placebo-controlled study could be ethically conducted in a population for whom universal vaccine is not recommended, have a sample size of reasonable proportions, and result in a firm estimate of vaccine efficacy. Use of culture confirmation as part of the case definition might allow for validation of a correlate of protection. Alternatively, a non-inferiority clinical endpoint study to a licensed influenza vaccine could be performed in a population for whom influenza vaccination is recommended. This approach would likely require a substantial sample size in order to be adequately powered. Influenza vaccine development would be greatly enhanced with the identification of an immunological correlate of protection.

- The sponsor would be required to perform additional safety and non-inferiority immunogenicity studies, or "bridging" immunogenicity studies, in the geriatric and pediatric populations. Particular attention would be given to the 6-23 month age group for whom universal vaccination is recommended. In this pediatric subgroup, the safety database should contain approximately 2,000 to 3,000 children. The total numbers in the geriatric age group

would depend on the robustness of the data from the studies submitted as part of the accelerated approval BLA. These additional studies will likely bring a total safety database to approximately 8,000 subjects, which would be sufficient for traditional approval. Studies conducted as confirmatory studies should include a safety evaluation at the 6-month post-vaccination timepoint.

- Vaccines and Related Biological Products Advisory Committee meeting was conducted on February 17, 2005 discussed the proposal for the use of the accelerated approval regulation including the presentation FluarixUS-001 phase 3 trial where HI titer analyses were used as surrogate endpoints that were reasonably likely to predict clinical benefit. The discussion among the VRBPAC members favored the accelerated approval approach outlined to them at the meeting.

- A teleconference on April 11, 2005 between CBER and GSK described difficulties in the preparation of the 1992 registrational study that would fulfill current electronic submission requirements. Instead, two recent clinical studies that were conducted as part of the yearly registration studies in Europe would fulfill current electronic submission requirements. CBER agreed to the submission of more recent studies, one conducted in 2004 and one conducted in 2002, that would provide additional safety and immune response data in adults over the age of 18 years of age, and would include a proportion of adults greater than 65 years of age. The two studies were viewed as supportive and not pivotal for the licensure of Fluarix.

6 Clinical Data Sources, Review Strategy, and Data Integrity

Material Reviewed:

- The final version of protocol FluarixUS-001 was submitted and reviewed in the BLA. The study was a placebo-controlled study with the primary endpoint of immune response following administration of Fluarix.
- The applicant submitted the results from three other studies, Fluarix-051, Fluarix-052, and Fluarix-058. Fluarix-052 was a randomized, active-control study conducted in adults greater than 60 years of age. Subjects were randomized to one of three influenza vaccines, Fluarix or one of two other licensed influenza vaccine products. Studies Fluarix-051 and Fluarix-058 were open-label, uncontrolled studies that were used to meet EMEA requirements for yearly licensure of influenza vaccine in European countries.
- Study FluarixUS-001 was considered to be an adequate and well-controlled study and enrolled adults 18-64 years of age.
- For all four studies, final study reports were reviewed as well as the clinical data in the form of [redacted] datasets. These included line listings for the adverse events and the HI antibody titer results.

BLA/NDA Volume Numbers Which Serve as a Basis for the Clinical Review:

- BLA number 125127 formed the basis for the clinical review. Safety data submitted to IND [redacted] in the form of spontaneous international adverse event reports, provided additional "post-marketing" safety data for the review.

Literature cited by the medical officer in this review:

[1] Hobson D, Curry RL, Beare AS, Ward-Gardner A. The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. J Hyg 1972;70:767-777.

[2] Treanor J, Keitel W, Belshe R, et al. Evaluation of a single dose of half strength inactivated influenza vaccine in healthy adults. Vaccine 2002;20:1099-1105.

Post-Marketing Experience:

- There are no post-marketing data from the United States. See section 5.3 for experience outside the United States.

Table 6.1: Table of Clinical Studies

Study	Country	Dates	Randomization	N	Lot numbers
FluarixUS-001	United States	Dec 04 - Jan 05	Fluarix:Placebo 4:1	956	AFLUA092C
Fluarix-052	Germany	Oct 02 - Jan 03	Fluarix:Fluad:Inflexal 1:1:1	827	18698A9
Fluarix-051	Germany	May 02 - Jun 02	Fluarix open-label	114	18698A9
Fluarix-058	Germany	Jun 04 - Jul 04	Fluarix open-label	120	AFLUA015A

Review Strategy

- Data from all four clinical trials were reviewed. In addition to the review of the final study reports, the [redacted] datasets were interrogated by using [redacted] software program. The rates of adverse events and results of immunogenicity parameters were calculated from the line listings provided in the [redacted] datasets and compared with the applicant's study results. Case report forms from serious adverse events were submitted and reviewed.

Good Clinical Practices (GCP) and Data Integrity

- The three studies conducted in Germany were carried out according to the Good Clinical Practice for the Clinical Testing of Medicinal Products in the European Community (CHMP/ICH/135/95) that has been valid in Germany as of January 18, 1998. The study in the United States was conducted in compliance with Good Clinical Practices, including the archiving of essential documents.
- As of July 15, 2005, a preliminary BIMO assessment from the field investigations of three clinical trials sites that conducted study FluarixUS-001 suggested that the data appeared to be acceptable.

Financial Disclosures

- None of the clinical investigators disclosed financial arrangements with the applicant.

7 Human Pharmacology

- Known human immunogenicity parameters and the potential relationship to prevention of influence illness are discussed above in sections 5.3 and 5.4.

8 Clinical Studies

Studies FluarixUS-001, Fluarix-052, Fluarix-051, and Fluarix-058 are discussed below.

8.1 Trial #1: "A randomized, double-blinded, placebo controlled phase III study to evaluate the immunogenicity and the safety of GSK Bio influenza vaccine (Fluarix) administered intramuscularly to healthy adults."

Applicant's Protocol Number: FluarixUS-001

Objective/Rationale:

- The primary objective was the determination of the immunogenicity parameters of the proportion of subjects with a four-fold or greater rise in HI antibody titers (seroconversion rate) and the proportion with HI antibody titer of greater than or equal to 1:40 following adminstration of Fluarix given intramuscularly in healthy adults approximately 21 days following vaccination. Secondary objectives included the determination of immunogenicity of Geometric Mean Titers (GMT) of Fluarix in healthy adults approximately 21 days following vaccination and the determination of safety and reactogenicity during the 21 days following intramuscular administration.

Design Overview:

- The study was a randomized, double-blind, placebo-controlled, multi-center study. Subjects received 0.5 ml of the trivalent influenza vaccine Fluarix given intramuscularly in the deltoid muscle of the non-dominant arm. Subjects were randomized 4:1, Fluarix to placebo. Subjects had blood draws for immune response at baseline and approximately 21 days following vaccination. After all subjects completed the 21 day study visit, study subjects were unblinded and subjects randomized to receive placebo were given an opportunity to receive Fluarix. The following table 8.1.1 represents the study overview:

Table 8.1.1: FluarixUS-001 study design

Visit	Blood for immune response	Day	Vaccine[1]	Route[2]	Site[3]	Side
1	X	0	*Fluarix*	IM	D	Non dominant
			or			
			Placebo	IM	D	Non dominant
2	X	21				
3*		28+	*Fluarix*	IM	D	Non dominant

[1]Vaccine/ Active Control to be blinded, [2]Intramuscular (IM), [3]Deltoid-non-dominant (D)
* Only for subjects in the placebo group

Population

- At least 525 healthy adult volunteers were planned for enrollment, with a maximum of 1050 healthy adult volunteers to be enrolled. Acute disease at the time of vaccination, defined as moderate or severe illness with or without fever (<37.5°C or <99.5°F) was listed as a contraindication to vaccination.

  Inclusion Criteria:

  - A male or female 18-64 years of age at the time of the vaccination.
  - Subjects who the investigator believes can and will comply with the requirements of the protocol (e.g., return for follow-up visit and completion of the diary cards) should be enrolled in the study.
  - Written informed consent obtained from the subject.
  - Free of obvious health problems as established by medical history and clinical examination before entering into the study.
  - Female subjects must be of non-childbearing potential, i.e. either surgically sterilized or one year post-menopausal. If subject is of childbearing potential, she must be abstinent or have used adequate contraceptive precautions (e.g. intrauterine contraceptive device; oral contraceptives or other equivalent hormonal contraception, e.g. progestogen-only implantable, cutaneous hormonal patch or injectable contraceptives, diaphragm or condom in combination with contraceptive jelly, cream or foam) for 30 days prior to vaccination. She must also have a negative pregnancy test at study entry and must agree to continue such precautions for two months after completion of vaccination.

  Exclusion Criteria:

  - Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) within 30 days preceding the administration of the study vaccine, or planned use during the study period.
  - Has received any other licensed vaccines within 2 weeks (for inactivated vaccines) or 4 weeks (for live vaccines) prior to enrollment in this study.

- ❑ Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within six months prior to the administration of the study vaccine. (For corticosteroids, this will mean prednisone, or equivalent, ≥ 0.5 mg/kg/day.)
- ❑ Any medically diagnosed or suspected immunodeficient condition based on medical history and physical examination (no laboratory testing required).
- ❑ Administration of immunoglobulins and/or any blood products within the three months preceding the administration of the study vaccine or during the study.
- ❑ History of hypersensitivity to a previous dose of influenza vaccine.
- ❑ History of allergy or reactions likely to be exacerbated by any component of the vaccine including egg, chicken protein, formaldehyde, gentamicin sulfate or sodium deoxycholate.
- ❑ Previous vaccination against influenza (2004-2005 influenza vaccine) within the 6 months prior to enrollment.
- ❑ Acute disease at the time of enrollment. (Acute disease is defined as the presence of a moderate or severe illness with or without fever. All vaccines can be administered to persons with a minor illness such as diarrhea, mild upper respiratory infection with or without low-grade febrile illness, i.e. Oral temperature <37.5°C (99.5°F) / Axillary temperature <37.5°C (99.5°F)).
- ❑ Acute clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests.
- ❑ Major congenital defects or serious chronic illness.
- ❑ History of any neurologic disorders or seizures, with the exception of a single febrile seizure during childhood.
- ❑ Pregnant or lactating female.
- ❑ Female planning to become pregnant or planning to discontinue contraceptive precautions within 2 months of enrollment in this study.
- ❑ Has an underlying medical condition for which influenza vaccination is recommended: chronic heart or lung conditions, including asthma; metabolic diseases; kidney disease; blood disorder (such as sickle cell anemia); weakened immune systems, including HIV/AIDS.
- ❑ 18 years of age and on chronic aspirin therapy
- ❑ Residents of nursing homes and long term care facilities.
- ❑ Health care workers involved in direct patient care.
- ❑ Out-of-home caregivers and household contacts of children <6 months.

- **Procedures not allowed:** Use of investigational products during the study period was not allowed, chronic administration of immunosuppressants during the study period was not allowed, and administration of another vaccine two weeks before for inactivated vaccine or four weeks before for live vaccine through the study period was not allowed.

Products mandated by the protocol:

- A 0.5 ml dose of Fluarix was administered to the non-dominant arm in the study. The vaccine contained HA from three influenza strains (total HA = 45 µg)
  A/ New Caledonia/20/99 (H1N1)-like strain: 15 µg
  A/Fujian/411/2002 (H3N2)-like strain: 15 µg
  B/Shangai/361/2002-like strain: 15 µg

  Fluarix contained the following excipients: sodium chloride, [redacted], alpha-tocopheryl hydrogen succinate, polysorbate 80 (Tween 80), octoxynol 9 (Triton X-100), and water. Fluarix was preservative-free, but contains residual levels of thimerosal from early stages of manufacturing, maximum thimerosal content was 0.0025 mg per dose. The lot number used in this trial was: Fluarix: Lot # AFLUA092C.

  The composition of placebo was [redacted]

Endpoints

- The co-primary endpoints were seroconversion rate with 95% CI at day 21 post-vaccination and proportion with HI antibody titers greater than or equal to 1:40 with 95% CI at day 21 post-vaccination, for each vaccine strain. Seroconversion rate with 95% CI at day 21 defined as the proportion of subjects with either a pre-vaccination HI antibody titer < 1:10 and a postvaccination antibody titer ≥ 1:40 or a pre-vaccination antibody titer ≥ 1:10 and a minimum four-fold increase in post-vaccination antibody titer.
- The immunogenicity criteria established by the CHMP of the EMEA listed in table 5.2 on page 10 in part formed the basis for the surrogate endpoints.
- The applicant proposed that the lower bound of the 95% confidence interval for seroconversion and proportion with HI antibody titer ≥1:40 for each of the three vaccine strains be above the EMEA immunogenicity criteria. Furthermore, each of the six endpoints, seroconversion and proportion with HI antibody titer ≥1:40 for each of the three vaccine strains, would have to be met.
- Secondary endpoints included geometric mean titers pre- and post-vaccination for each vaccine strain with 95% confidence intervals, conversion factors for each vaccine strain defined as the fold increase in GMT on day 21 compared to day 0, and proportion with four-fold increase in HI antibody titer if baseline titer is < 1:40 (excluding subjects with baseline titers ≥ 1:40).

- Safety evaluations were tabulated as secondary endpoints. This included the percentage, intensity, and relationship to vaccination for local and systemic adverse events, both solicited and unsolicited adverse events. The occurrence of serious adverse events would be tabulated.
- The HI antibody titers were measured on thawed serum samples with a standardized method using 4 hemagglutinin-inhibiting units of the appropriate antigens and 0.5% fowl erythrocyte suspension. The antibody titers were performed at GSK Biological's central laboratory in Dresden, Germany. Starting with an initial dilution of 1:10, dilution series by a factor of 2 was prepared up to an end dilution of 1:20480. The titration endpoint was the highest dilution step that showed complete inhibition of hemagglutination. All assays were performed in duplicate.

Reviewer Comment: The pre-defined criteria for success were more robust in comparison to the EMEA immunogenicity criteria. The EMEA requires only one endpoint be achieved in order to be considered successful. The assay used to determine HI antibody titers was subject to variability among and within laboratories. However, the applicant submitted the results of an assay validation package to the IND prior to the assays being run for this study at the Dresden, Germany facility. The assay information was reviewed by CBER product reviewers and statisticians and, with some requests and comments for modification, found to be acceptable (for details see CMC review). The use of the HI antibody titers was reasonably likely to predict clinical benefit.

Surveillance/Monitoring

- Demographic data, medical history including influenza vaccination history, directed physical examination "if deemed necessary", urine pregnancy test if female, blood draw for baseline immune response parameters, and baseline body temperature, and a check for potential contraindications to vaccination were performed before vaccination. Subjects were monitored for 30 minutes immediately following vaccination. Subjects were given a diary card and instructed to record solicited adverse events for three days post-vaccination and record unsolicited adverse events for 20 days post-vaccination, with instructions to call the investigator immediately for any adverse events perceived as serious. Subjects returned at approximately 21 days following receipt of vaccine in order to obtain blood draw for immunogenicity parameters, collection and review of diary card, recording of other medications, and recording of unsolicited symptoms that may have occurred after vaccination. This visit concluded the "active" phase of the study.

- Subjects were then unblinded and those randomized to placebo were contacted to return to the clinic for open-label vaccination with Fluarix, if subjects desired. For subjects initially randomized to placebo who received open-label Fluarix after unblinding, only unsolicited symptoms that required medical attention for at least 21 days after vaccination with Fluarix were recorded. That is, solicited adverse events were not recorded in a systematic way,

except as part of the initial blinded phase of the study during which they would have received placebo. The intensity scales for solicited symptoms are described in the following table:

Table 8.1.2: Intensity scales for solicited symptoms in adults

Adverse event	Intensity grade	Parameter
Pain at injection site, headache, fatigue, joint pain (arthralgia), muscle ache (myalgia), shivering	0	Absent
	1	Is easily tolerated
	2	Interferes with normal activity
	3	Prevents normal activity
Redness/swelling at injection site	0	0 mm
	1	> 0 - ≤ 20 mm
	2	> 20 - ≤ 50 mm
	3	> 50 mm
Fever	0	< 37.5ºC
	1	≥ 37.5 - ≤ 38.0ºC
	2	> 38.0 – 39.0ºC
	3	> 39.0ºC

Reviewer Comment: There was no active surveillance for influenza infection by culture or other clinical sampling. Symptoms of influenza-like illness, use of anti-influenza antivirals, or diagnosis of influenza illness were recorded at the day 21 study visit. The study did not have power to detect a difference between the groups in terms of the proportions with clinical disease due to influenza.

Statistical considerations for Study FluarixUS-001

- For each vaccine strain, the proportion with at least a four-fold rise in HI antibody titer and the proportion with HI antibody titer of at least 1:40 were calculated and were regarded as co-primary endpoints. Secondary endpoints included the calculation of GMTs before and after vaccination, the fold-increase in serum HI GMT on day 21 compared to baseline, and proportion with a four-fold increase if the baseline titer is less than 1:40. Safety was also a secondary endpoint.
- The sample size was calculated assuming a point estimate of the proportion with at least a four-fold rise in HAI titer of 55.4%, with a two-sided 95% confidence interval and a 10% response rate in the placebo group. The applicant stated that the study would have greater than 95% power if the sample size contained at least 400 persons in the Fluarix group and at least 100 persons in the placebo group. A description of the sample size calculations from the protocol:

A Fisher's exact test with a 0.05 two-sided significance level will have 99% power to detect the difference between a *Fluarix* seroconversion rate of 55.4% and a *Placebo* seroconversion rate of 10% when the sample size is 400 and 100 evaluable subjects respectively in *Fluarix* and *Placebo* [redacted] group.
A Fisher's exact test with a 0.05 two-sided significance level will have 99% power to detect the difference between a *Fluarix* seroprotection rate of 87.5% and a *Placebo* seroprotection rate of 20% when the sample size is 400 and 100 evaluable subjects respectively in *Fluarix* and *Placebo* [redacted] group.

Reviewer Comment: For all six endpoints, where each endpoint has 99% power, is $0.99^{(6)}$ and equals 94% in contrast to the applicant's "greater than 95% power". Nevertheless, the study appeared to be adequately powered for all six endpoints. Please refer to section 5.4, Regulatory Background Information, for additional discussion of the study's statistical analysis plan and CBER's point of view that the statistical analysis plans were acceptable.

- The "according-to-protocol" (ATP) cohort for the analysis of immunogenicity includes all subjects who meet eligibility criteria, complied with study procedures, and data measures from at least one vaccine strain were available. The ATP cohort for analysis of safety included subjects who received vaccine and did not receive a vaccine not specified in the protocol. However, safety was analyzed first by the "total vaccinated" cohort and if this cohort differed by more than 5% of the ATP cohort, both cohorts would be evaluated for safety endpoints. Medically attended adverse events and serious adverse events were evaluated by telephone contact approximately 21 days after receipt of Fluarix for subjects who initially received placebo and returned to receive open-label Fluarix.
- GSK randomized subjects to Fluarix: placebo at 4:1 by an internet randomization software program. The randomization accounted for study sites and subject age. Subjects were stratified by age group above or below age 50 years: approximately 2/3 were below 50 years, and 1/3 were above 50 years of age. The subjects, investigators, and GSK medical monitors were blinded to what was received until the end of the active study phase at day 21 and once the data from the sites are received and the database has been locked.

Results, study FluarixUS-001

Populations enrolled and analyzed

- The total number of subjects enrolled at clinical trial sites in the United States was 956; 763 were randomized to receive Fluarix and 193 were randomized to receive placebo. The first subject enrolled December 13, 2004, and the last study visit of the last subject enrolled was January 14, 2005. The following table summarized the applicant's report of the population enrolled and population considered for analysis:

Table 8.1.3: Population FluarixUS-001

	Group		
	Fluarix	Placebo	Total
Number of subjects enrolled	**763**	**193**	**956**
Number of subjects vaccinated	760	192	952
Number of subjects completed	759	191	950
Number of subjects withdrawn	4	2	6
Reasons for withdrawal:			
Subject enrolled but not vaccinated	3	1	4
Serious adverse event	1	0	1
Lost to follow-up	0	1	1
Total vaccinated cohort	**760**	**192**	**952**
Administration of vaccine not permitted according to protocol	3	0	3
Study vaccine dose not administered according to protocol	3	1	4
Non-compliance with blood sampling schedule	7	0	7
Essential serological data missing	2	1	3
ATP immunogenicity cohort	**745**	**190**	**935**
ATP safety cohort	**754**	**191**	**945**

Reviewer comment: there were very few subjects who withdrew or were lost to follow up in this study. Two study subjects received licensed influenza vaccine during the study and one subject received tetanus vaccine. Interrogation of the BLA databases confirmed the applicant's above calculations of the population cohorts.

- A total of 18 subjects were reported by the applicant in the datasets to be screened but not enrolled in the study and therefore not included in the subject enrollment tables. Eight had a history of allergic reactions to medications or seasonal allergies that met exclusion criteria, seven had skin, joint, or other disorders that might affect the interpretation of adverse events, and three had acute upper respiratory tract infections.

Table 8.1.4 Demographic characteristics Study FluarixUS-001

Total vaccinated cohort		Fluarix n=760	Placebo n=192	Total n=952
Characteristic	Parameters or categories	Value or N (%)	Value or N (%)	Value or N (%)
Age	Mean	39.1	39.1	39.1
	Standard dev.	13.15	13.32	13.2
	Median	38	39	38
	Minimum/maximum	18/64	18/64	18/64
Gender	Female	408 (54%)	107 (56%)	515 (54%)
	Male	352 (46%)	85 (44%)	437 (46%)
Race	White/Caucasian	605 (80%)	155 (81%)	760 (80%)
	Black	89 (12%)	18 (9%)	107 (11%)
	Hispanic	13 (2%)	4 (2%)	17 (2%)
	Asian	44 (6%)	11 (5%)	55 (6%)
	Other	9 (1%)	4 (2%)	12 (1%)

Seventeen subjects did not comply with the study procedures and were eliminated from the ATP vaccinated cohort. Thirteen subjects were White/Caucasian and three were Black, therefore the demographics of the ATP cohort did not differ substantially from the demographics of the total vaccinated cohort. Seven subjects were not available for follow up of safety. The demographics of the safety cohort did not differ from the total vaccinated cohort.

Table 8.1.5 Enrollment by study center

Study center	Fluarix	Placebo	Total
11536	222	56	278
11537	180	45	225
11566	212	54	266
11593	148	37	185
Total	762	192	954

Reviewer comment: enrollment was generally equally distributed. A disproportionate amount of enrollment did not occur at one or more study centers.

Table 8.1.6 Study day that subjects received the "day 21" study visit blood draw

Study day	Fluarix	Placebo	Total
20	6	0	6
21	628	163	791 (83.3%)
22	59	15	74
23	9	3	12
24	22	4	26
25	18	2	20
26	9	0	9
27	4	3	7
28	4	1	5

Reviewer comment: the majority of study subjects had sera drawn for the HI antibody titers at day 21 of the study, and included subjects who had sera drawn out to day 28.

Table 8.1.7 A total of 551 subjects had data that recorded whether receipt of influenza vaccine had occurred in the one or more of the preceding three years 2001, 2002, and 2003

Year	Fluarix N=760		Placebo N=192		Total N=952	
	Yes (%)	No (%)	Yes (%)	No (%)	Yes (%)	No (%)
2001	273 (36)	178 (23)	61 (32)	39 (20)	334 (35)	217 (23)
2002	302 (40)	149 (20)	64 (33)	36 (19)	366 (38)	185 (19)
2003	311 (41)	140 (18)	77 (40)	23 (12)	388 (41)	163 (17)

Reviewer comment: Roughly the same proportion of study subjects reported receipt of vaccine in either of the years previous between placebo and Fluarix groups. A total of 401 subjects did not report previous receipt of influenza vaccine recorded on the case report form.

Table 8.1.8 The numbers and the ratios of the past medical history by group outlined below

Diagnostic group	Fluarix	Placebo	Ratio
Total vaccinated cohort	760	192	**4.0**
Allergies	318 (42%)	67 (35%)	4.7
Cardiovascular	147 (19%)	38 (20%)	3.9
Cutaneous	103 (14%)	31 (16%)	3.3
Ear-nose-throat	134 (18%)	37 (19%)	3.6
Endocrine	52 (7%)	10 (5%)	5.2
Eyes	120 (16%)	32 (17%)	3.6
Gastrointestinal	144 (19%)	42 (22%)	3.4
Genito-urinary	202 (27%)	53 (28%)	3.8
Hematology	25 (3%)	8 (4%)	3.1
Musculoskeletal	232 (31%)	64 (33%)	3.6
Neurological	96 (13%)	25 (13%)	3.8
Respiratory	34 (4%)	15 (8%)	2.3
Other	120 (16%)	24 (13%)	5.0
Total line listings	1727	446	3.9

Reviewer comment: The data were derived from the applicant's dataset, and absolute numbers, percentages, and ratios were calculated by the reviewer. Each subject may have contributed more than one diagnostic group on the case report form. Therefore, the data are presented as a ratio of absolute numbers as well as percentages, using the total vaccinated cohort as a denominator. There appear to be similar proportions of past medical history between the treatment groups.

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

- The sponsor provided the seroconversion rates i.e., either a pre-vaccination HI antibody titer < 1:10 and a post-vaccination titer ≥ 1:40, or a pre-vaccination titer ≥ 1:10 and a minimum four-fold increase in post-vaccination titer, are shown in the following table 8.1.9:

Table 8.1.9 Seroconversion numbers and rates at day 21 (ATP cohort for Immunogenicity)

Antibody	Group	N	Responders			
					95% CI of rate	
			n	%	LL	UL
A/New Caledonia (H1N1)	Fluarix	745	444	59.6	56.0	63.1
	Placebo	190	0	0	0	1.9
A/Wyoming (H3N3)	Fluarix	745	461	61.9	58.3	65.4
	Placebo	190	2	1.1	0.1	3.8
B/Jiangsu	Fluarix	745	578	77.6	74.4	80.5
	Placebo	190	2	1.1	0.1	3.8

The lower bound of the 95% confidence interval exceeded the pre-specified criteria set forth in the data analysis plan.

Table 8.1.10 The numbers and proportion with HI antibody titer ≥1:40 for the vaccine strains at pre- and post-vaccination

Antibody	Group	Timing	Proportion with HAI titer ≥1:40				
						95% CI of proportion	
			N	N	%	LL	UL
A/New Caledonia (HIN1)	Fluarix	PRE	745	408	54.8	51.1	58.4
		PI(D21)	745	720	96.6	95.1	97.8
	Placebo	PRE	190	99	52.1	44.8	59.4
		PI(D21)	190	97	51.1	43.7	58.4
A/Wyoming (H3N2)	Fluarix	PRE	745	512	68.7	65.3	72.0
		PI(D21)	745	738	99.1	98.1	99.6
	Placebo	PRE	190	124	65.3	58.0	72.0
		PI(D21)	190	124	65.3	58.0	72.0
B/Jiangsu	Fluarix	PRE	745	369	49.5	45.9	53.2
		PI(D21)	745	736	98.8	97.7	99.4
	Placebo	PRE	190	93	48.9	41.6	56.3
		PI(D21)	190	97	51.1	43.7	58.4

Reviewer Comment: The lower bound of the 95% confidence intervals exceeded the pre-specified criteria (CHMP) set forth in the data analysis plan.

The applicant presented the results of secondary analyses in the following tables:

Table 8.1.11 Geometric mean titers (GMT) for HI antibody titers at pre- and post-vaccination

Antibody	Group	Timing	N	Value	95% CI of GMT	
					LL	UL
A/New Caledonia (HIN1)	Fluarix	PRE	745	43.0	38.2	48.3
		PI(D21)	745	438.3	393.1	488.6
	Placebo	PRE	190	43.0	34.0	54.5
		PI(D21)	190	44.9	35.5	56.8
A/Wyoming (H3N2)	Fluarix	PRE	745	61.9	56.3	68.0
		PI(D21)	745	425.0	393.1	459.5
	Placebo	PRE	190	53.5	44.4	64.6
		PI(D21)	190	55.8	46.4	67.2
B/Jiangsu	Fluarix	PRE	745	32.6	29.9	35.5
		PI(D21)	745	337.7	314.0	363.2
	Placebo	PRE	190	30.4	25.6	36.2
		PI(D21)	190	32.7	27.4	39.0

Table 8.1.12 The number and proportion of subjects with baseline HI antibody titers of <1:40 who had four-fold increase in HI antibody titer

Antibody	Group	N	Responders			
			n	%	95% CI of proportions LL	UL
A/New Caledonia (H1N1)	Fluarix	344	293	85.2	81.0	88.8
	Placebo	92	1	1.1	0	5.9
A/Wyoming (H3N3)	Fluarix	239	223	93.3	89.5	96.1
	Placebo	67	2	3.0	0.4	10.4
B/Jiangsu	Fluarix	384	361	94.0	91.1	96.2
	Placebo	98	2	2.0	0.2	7.2

Table 8.1.13: The applicant's results of a secondary analysis of seroconversion numbers and rates among adults ages 50-64 who fulfilled criteria for the ATP cohort

Antibody	Group	N	Responders			
					95% CI of rates	
			n	%	LL	UL
A/New Caledonia (H1N1)	Fluarix	210	88	41.9	35.2	48.9
	Placebo	53	0	0	0	6.7
A/Wyoming (H3N3)	Fluarix	210	110	52.4	45.4	59.3
	Placebo	53	1	1.9	0	10.1
B/Jiangsu	Fluarix	210	141	67.1	60.3	73.5
	Placebo	53	0	0	0	6.7

Reviewer comment: the results from the applicant's subgroup of study participants ages 50-64 show a less robust immune response in this subgroup. The point estimates were within the CHMP criteria for adults ages 18-60 years of age for each of the three antigens, and the lower bound of the 95% confidence intervals were within the CHMP criteria for adults greater than 60 years of age.

- The following represents a summary of Dr. Sang Ahnn's summary of the statistical review of the efficacy endpoints:

Tables 8.1.14 and 8.1.15 show the primary immunogenicity results (based on per-protocol analyses). Dr. Ahnn confirmed all the numbers in the tables.

Table 8.1.14. Seroconversion rate at post-vaccination Day 21

Antibody	Group	N	Seroconversion Rate	95% CI of rates
H1N1	Fluarix	745	59.6%	(56.0%, 63.1%)
	Placebo	190	0.0%	(0.0%, 1.9%)
H3N2	Fluarix	745	61.9%	(58.3%, 65.4%)
	Placebo	190	1.1%	(0.1%, 3.8%)
B	Fluarix	745	77.6%	(74.4%, 80.5%)
	Placebo	190	1.1%	(0.1%, 3.8%)

Table 8.1.15. Percentage of subjects with serum HI antibody titer ≥1:40 at post-vaccination Day 21

Antibody	Group	N	% of subjects w/ HI titer ≥1:40	95% CI of rates
H1N1	Fluarix	745	96.6%	(95.1%, 97.8%)
	Placebo	190	51.1%	(43.7%, 58.4%)
H3N2	Fluarix	745	99.1%	(98.1%, 99.6%)
	Placebo	190	65.3%	(58.0%, 72.0%)
B	Fluarix	745	98.8%	(97.7%, 99.4%)
	Placebo	190	51.1%	(43.7%, 58.4%)

Reviewer Comment: Dr. Ahnn, the statistical reviewer, confirmed the results of the primary endpoints of seroconversion rate and proportion of subjects with HI antibody titer of ≥1:40.

A review of the proportion with serum HI titers ≥1:40 post vaccination among the four study sites is summarized in the table below.

Table 8.1.16 Analysis of the endpoint of percentage of subjects with HAI titer ≥1:40 among the four different study sites

		Study sites			
	Total	11536	11537	11566	11593
Total N	952	278	225	264	185
Seroname					
A/Wyoming					
Fluarix	99.1%	99.5%	99.4%	96.7%	100%
Placebo	65.3%	62.5%	60.0%	68.5%	67.6%
A/New Caledonia					
Fluarix	96.6%	95.9%	94.4%	97.1%	98.6%
Placebo	51.1%	53.6%	48.9%	42.6%	59.5%
B/Jiangsu					
Fluarix	98.8%	99.0%	99.4%	97.6%	98.6%
Placebo	51.1%	48.2%	53.3%	53.7%	45.9%

Reviewer comment: there did not appear to be differences in the primary endpoint of proportion of subjects with HAI titer ≥1:40 among the four different study sites.

Safety outcomes

Review of the applicant's summary adverse events:

- Serious Adverse Events: There was one serious adverse event that was reported in the study. This was a death due to atherosclerotic cardiovascular disease, although an autopsy was not performed. The death occurred 17 days after vaccination with Fluarix. The subject reported feeling well up to and at least two days before his death. The subject reportedly tolerated the vaccination without report of local or systemic adverse event.

Narrative by the applicant of the SAE reported in the study:
This 59-year-old male subject was enrolled in a blinded study (104233) for prophylaxis of influenza. It was reported that the subject most likely had diabetes and underlying heart disease. The subject also had a medical history of smoking. On [redacted] the subject received intramuscular investigational product single dose in the left arm. The subject had been randomized to receive the investigational product, trivalent [HA from three influenza strains (total HA = 45 µg): A/ New Caledonia/20/99 (HIN1)-like

strain (15 µg); A/Fujian/411/2002 (H3N2)-like strain (15 µg); B/Shangai/361/2002-like strain (15 µg)] inactivated split virion influenza vaccine (Fluarix for the Northern Hemisphere 2004-2005 influenza season). Lot number was AFLUA092C.
On [redacted] 17 days after the first dose of investigational product, this 59-year old subject died; cause of death was reported as atherosclerotic cardiovascular disease. It was reported that the subject tolerated the investigational product "quite well", and he was reported to still be "well" at least two days before he died. An autopsy was not performed. Per the Death Certificate, smoking probably contributed to the cause of death. It was reported that the medical information recorded on the Death Certificate was obtained from the subject's next of kin (half-brother) and not from medical records. The investigator considered there was no reasonable possibility that the fatal event of atherosclerotic cardiovascular disease may have been caused by investigational product. The investigator also considered the fatal event of atherosclerotic cardiovascular disease to be possibly associated with the medical condition of diabetes mellitus.

The applicant summarized the adverse event reports in tabular format.

Table 8.1.17 Number, rate, and nature of symptoms (solicited and unsolicited) reported during the 3 day follow-up period and overall (Total Vaccinated Cohort)

		Symptoms					General					Local				
		N	n	%	95% CI of rate		N	n	%	95% CI of rate		N	n	%	95% CI of rate	
					LL	UL				LL	UL				LL	UL
Overall/ subject	Fluarix	760	540	71.1	67.7	74.3	760	347	45.7	42.1	49.3	760	460	60.5	57.0	64.0
	Placebo	192	97	50.5	43.2	57.8	192	77	40.1	33.1	47.4	192	48	25.0	19.0	31.7

Table 8.1.18 Number, rate, and nature of grade 3 symptoms (solicited and unsolicited) reported during the 3 day follow-up period and overall (Total Vaccinated Cohort)

		Symptoms					General					Local				
		N	n	%	95% CI of rate		N	n	%	95% CI of rate		N	n	%	95% CI of rate	
					LL	UL				LL	UL				LL	UL
Overall/ subject	Fluarix	760	9	1.2	0.5	2.2	760	8	1.1	0.5	2.1	760	2	0.3	0.0	0.9
	Placebo	192	5	2.6	0.9	6.0	192	5	2.6	0.9	6.0	192	0	0.0	0.0	1.9

Applicant's summary of solicited adverse events. The applicant provided in tabular format the number and proportions of subjects who reported solicited adverse events.

Table 8.1.19 Number and rate of solicited local symptoms reported during the 3 day follow-up period (Total Vaccinated Cohort)

Group		Fluarix					Placebo				
		N	n	%	95% CI of rate		N	n	%	95% CI of rate	
					LL	UL				LL	UL
PAIN	Any	760	416	54.7	51.1	58.3	192	23	12.0	7.7	17.41.9
	Grade 3	760	1	0.1	0.0	0.7	192	0	0.0	0.0	
REDNESS	Any	760	133	17.5	14.9	20.4	192	20	10.4	6.5	15.61.9
	Grade 3	760	0	0.0	0.0	0.5	192	0	0.0	0.0	
SWELLING	Any	760	71	9.3	7.4	11.6	192	11	5.7	2.9	10.01.9
	Grade 3	760	1	0.1	0.0	0.7	192	0	0.0	0.0	

Table 8.1.20 Number and rate of solicited general symptoms reported during the 3 day follow-up period (Total Vaccinated Cohort)

Group		Fluarix				Placebo			
		n	%	95% CI of rate		n	%	95% CI of rate	
				LL	UL			LL	UL
N		760				192			
ARTHRALGIA (joint pain)	Any	49	6.4	4.8	8.4	12	6.3	3.3	10.7
	Grade 3	1	0.1	0.0	0.7	1	0.5	0.0	2.9
	Rel	47	6.2	4.6	8.1	12	6.3	3.3	10.7
	Grade 3*Rel	1	0.1	0.0	0.7	1	0.5	0.0	2.9
FATIGUE	Any	150	19.7	17.0	22.7	34	17.7	12.6	23.9
	Grade 3	3	0.4	0.1	1.1	2	1.0	0.1	3.7
	Rel	144	18.9	16.2	21.9	30	15.6	10.8	21.5
	Grade 3*Rel	3	0.4	0.1	1.1	2	1.0	0.1	3.7
FEVER	Any	13	1.7	0.9	2.9	3	1.6	0.3	4.5
	Grade 3	0	0.0	0.0	0.5	0	0.0	0.0	1.9
	Rel	10	1.3	0.6	2.4	1	0.5	0.0	2.9
	Grade 3*Rel	0	0.0	0.0	0.5	0	0.0	0.0	1.9
HEADACHE	Any	147	19.3	16.6	22.3	41	21.4	15.8	27.8
	Grade 3	1	0.1	0.0	0.7	2	1.0	0.1	3.7
	Rel	137	18.0	15.4	20.9	38	19.8	14.4	26.1
	Grade 3*Rel	1	0.1	0.0	0.7	2	1.0	0.1	3.7
MYALGIA (MUSCLE ACHES)	Any	175	23.0	20.1	26.2	23	12.0	7.7	17.4
	Grade 3	3	0.4	0.1	1.1	1	0.5	0.0	2.9
	Rel	172	22.6	19.7	25.8	22	11.5	7.3	16.8
	Grade 3*Rel	3	0.4	0.1	1.1	1	0.5	0.0	2.9
SHIVERING	Any	25	3.3	2.1	4.8	5	2.6	0.9	6.0
	Grade 3	1	0.1	0.0	0.7	0	0.0	0.0	1.9
	Rel	24	3.2	2.0	4.7	5	2.6	0.9	6.0
	Grade 3*Rel	1	0.1	0.0	0.7	0	0.0	0.0	1.9

Reviewer comment: The applicant did not provide tests of significance for the adverse event rates.

❑ Medical officer review of solicited adverse events during the 21 days post-vaccination. Approximately 507 subjects reported at least one solicited adverse event during the study. The denominator used in the calculation of the percentage of study participants experiencing the adverse event was the total vaccinated cohort of 760 subjected who received Fluarix and 192 subjects who received placebo. The following tables represent the proportions of solicited adverse events in the study:

Table 8.1.21 Clinical review of the safety datasets submitted to the BLA. *The proportions that differed between the medical officer review and the applicant are in italics*:

Local Redness	**Fluarix (n=760)**	**Placebo (n=192)**	**Total (n=952)**
Grade 1	129	19	148
Grade 2	4	1	5
Grade 3	0	0	0
Total Redness	**133 (17.5%)**	**20 (10.4%)**	**152 (16.1%)**
Applicant same			
Local swelling			
Grade 1	63	10	73
Grade 2	7	1	8
Grade 3	2	0	2
Total swelling	**72 (9.5%)**	**11 (5.7%)**	**83 (8.7%)**
Applicant same			
Local pain			
Grade 1	396	22	418
Grade 2	26	1	27
Grade 3	1	0	1
Total pain	**423 (55.6%)**	**23 (12.0%)**	**446 (46.8%)**
Applicant	***416 (54.7%)***	***23 (12.0%)***	
Fatigue			
Grade 1	110	23	133
Grade 2	42	6	48
Grade 3	1	2	3
Total fatigue	**153 (20.1%)**	**31 (16.1%)**	**184 (19.3%)**
Applicant	***150 (19.7%)***	***34 (17.7%)***	
Headache			
Grade 1	110	34	144
Grade 2	36	5	41
Grade 3	1	2	3
Total headache	**147 (19.3 %)**	**41 (21.4%)**	**188 (19.7%)**
Applicant	***149 (19.3%)***	***41 (21.4%)***	
Continued on	**next page**		

Table 8.2.21, cont.	Fluarix	Placebo	Total
Muscle aches			
Grade 1	144	20	164
Grade 2	28	2	30
Grade 3	4	0	4
Total muscle aches	**176 (23.2%)**	**22 (11.5%)**	**198 (20.8%)**
Applicant	***175 (23.0%)***	***23 (12.0%)***	
Shivering			
Grade 1	17	6	23
Grade 2	7	0	7
Grade 3	0	0	0
Total shivering	**24 (3.2%)**	**6 (3.1%)**	**30 (3.2%)**
Applicant	***25 (3.3%)***	***5 (2.6%)***	
Joint pain			
Grade 1	33	11	44
Grade 2	13	1	14
Grade 3	0	3	3
Total joint pain	**46 (6.1%)**	**15 (7.8%)**	**61 (6.4%)**
Applicant	***49 (6.4%)***	***12 (6.3%)***	
Fever			
Grade 1	8	2	10
Grade 2	2	0	2
Grade 3	0	0	0
Total fever	**10 (1.3%)**	**2 (1.0%)**	**12 (1.3%)**
Applicant	***13 (0.9%)***	***3 (1.6%)***	

Reviewer Comment: The applicant was asked on a July 8, 2005 teleconference to provide a confirmation of the percentages of solicited adverse events to be used in the Adverse Events section of the label. On July 11, 2005 the applicant confirmed the percentages in the original BLA. Because the percentages did not differ substantially, and the software programs used in the analyses of adverse events may elicit some minor differences between CBER and the applicant, the reviewer feels comfortable accepting the analysis of adverse events from the applicant.

There were approximately 449 study subjects who did not report solicited adverse events. Of these 449 study subjects, 133 subjects reported 234 unsolicited adverse events. The following table represents important adverse events that were discovered in the unsolicited adverse events among subjects that lacked reported solicited adverse events:

Table 8.1.22 Selected mild or moderate adverse events among 133 subjects that had no reports of solicited adverse events during the 21 day post-vaccination follow-up (adverse event reported as grade 3 or severe noted in table)

Adverse event	Fluarix	Placebo	Total
Arthralgias*	2	2	4
Fever (pyrexia)*	2	1	3
Headache*	36 (4 grade 3)	16 (1 grade 3)	52 (5 grade 3)
Shivering (chills)*	2	1	3
* = events that might have been reported in the solicited adverse events, occurred after day 3			
Cough	5	5	19
Pharyngolaryngeal pain	5	5	10
URI	11	3	14
Other various AE not greater than 5 per group	72	45	117

Therefore, 316 study participants (33%) did not report an adverse event at all during the study. A total of 220 (29%) subjects who received Fluarix and 94 (49%) subjects who received placebo did not report an adverse event.

The applicant summarized the unsolicited adverse event data, and stated that the most commonly reported unsolicited adverse events among recipients of Fluarix and placebo, respectively, were headaches (9.9% and 8.3%), upper respiratory infections (3.9% and 2.6%), and pharyngolaryngeal pain (2.6% and 4.7%). The applicant reported that the percentage of unsolicited adverse events reported to be causally related to vaccination was 7.9% in the Fluarix group and 8.3% in the placebo group. Of the grade 3 adverse events, the most commonly reported were diarrhea, vomiting, and headaches. Grade 3 diarrhea occurred in 1.3% of Fluarix recipients, 0% in placebo recipients; grade 3 vomiting occurred in 1.1% of Fluarix recipients, 0% in placebo recipients; grade 3 headaches occurred in 0.8% of Fluarix recipients, 1.0% placebo recipients.

- Medical officer review of the unsolicited adverse events during the 21 days post-vaccination. There were 644 line listing reports of unsolicited adverse events among 345 study subjects:

Table 8.1.23 Unsolicited adverse events

Adverse Event Category All line listings	Fluarix	Placebo	Total
Blood and lymphatic system disorder	3	0	3
Cardiac disorder	1	0	1
Ear and labyrinth disorder	3	1	4
Endocrine disorder	1	0	1
Eye disorder	6	0	6
Gastrointestinal disorder	55	8	63
General disorders and administration site conditions	60	10	70
Immune system disorder	5	0	5
Infectious and infestations	76	16	92
Injury, poisoning, and procedural complications	14	1	15
Metabolism and nutrition disorders	1	0	1
Musculoskeletal and connective tissue disorders	48	11	59
Nervous system disorder	118	22	140
Psychiatric disorder	4	0	4
Renal and urinary disorders	10	2	12
Reproductive system and breast disorders	10	2	12
Respiratory, thoracic, and mediastinal disorders	99	37	136
Skin and subcutaneous disorders	9	4	13
Surgical and medical procedures	4	0	4
Vascular disorders	3	0	3
Total number	530	114	644

Analysis of the more commonly reported unsolicited adverse events:

Table 8.1.24 Gastrointestinal disorders

Adverse event	Fluarix	Placebo	Total
Nausea	13	3	16
Vomiting	11	1	12
Diarrhea	13	0	13
Other GI	18	4	22
			63

Reviewer Comment: A somewhat greater proportion of subjects reported diarrhea or vomiting as adverse events in comparison to the placebo group, while none of the other gastrointestinal disorder appeared be reported with different frequencies.

Table 8.1.25 General disorders and administration site conditions

Adverse event	Fluarix	Placebo	Total
Fatigue	14	2	16
Influenza like illness	12	1	13
Injection site reaction, pain, tenderness, etc.	18	5	23
Pyrexia	5	1	6
Other	11	1	12
			70

Table 8.1.26 Infections

Adverse event	Fluarix	Placebo	Total
URI	32	6	38
Nasopharyngitis	19	3	22
Other	25	7	32
			92

Table 8.1.27 Musculoskeletal and connective tissue disorders

Adverse event	Fluarix	Placebo	Total
Myalgia	15	4	19
Arthralgias	7	2	9
Neck pain/pain in extremity/ back pain	20	5	25
Other	6	0	6
			59

Table 8.1.28 Nervous system disorders

Adverse event	Fluarix	Placebo	Total
Headache	102	22	124
Migraine	6	0	6
Other	10	0	10
			140

Reviewer comment: A further analysis of ten subjects who experienced "other" nervous system adverse events was undertaken because all occurred in the Fluarix arm. Four subjects reported sinus headache 4-8 days after vaccination, all grade 2, all lasting one or two days and were all characterized as resolved. Four subjects reported dizziness. One subject experienced grade 2 "lightheadedness" which occurred just after administration of vaccine and resolved in one day. One subject experienced grade 1 dizziness three days after vaccine along with grade 2 nausea and vomiting, and resolved in one day. These two events were judged by the study investigator to be related to vaccination. Two other subjects experienced dizziness with URI symptoms or headache, occurred two weeks after vaccination, and were judged by the study investigator to be not related to vaccine. All resolved by the day 21 study visit. One subject experienced metallic taste, which was characterized as resolved. Lastly, one subject experienced "paraesthesias" (grade 1) and "myalgias" (grade 2) of the right arm approximately 14 days following vaccination. The subject reported the event at the day 21 visit. No medical intervention was sought and the event was characterized as "not resolved" at that visit. The investigator judged the event to be unrelated to vaccination and no further clinical data were provided.

Table 8.1.29 Respiratory, thoracic, and mediastinal disorders

Adverse event	Fluarix	Placebo	Total
Pharyngolaryngeal pain	23	9	32
Nasal congestion	18	5	23
Cough	19	8	27
Rhinorrhea	9	6	15
Sinus congestion	11	4	15
Other	19	5	24
			136

Table 8.1.30 List of unsolicited events that were characterized as grade 3 adverse events

Adverse event	Fluarix	Placebo	Total
Diarrhea*	10	0	10
Vomiting	8	0	8
Headache*	6	2	8
Influenza like illness*	6	0	6
Migraine*	5	0	5
Fatigue	4	0	4
URI	3	1	4
Gastroenteritis	3	0	3
Nausea*	2	1	3
Bronchitis	2	0	2
Myalgias	1	1	2
Pharyngolaryngeal pain	1	1	2
Sinus congestion	1	1	2
Pyrexia	2	0	2
Abdominal pain	2	0	2
Atherosclerosis	1	0	1
Atrial tachycardia	1	0	1
Back pain	1	0	1
Carpal tunnel	1	0	1
Corneal abrasion	1	0	1
Cough	1	0	1
Dyspepsia	1	0	1
Food poisoning	1	0	1
Ganglion	1	0	1
Gastrointestinal disorder	0	1	1
Gastrointestinal infection	1	0	1
Muscle cramp	1	0	1
Nasal congestion	0	1	0
Nephrolithiasis	0	1	0

Table 8.1.30, cont.	Fluarix	Placebo	Total
Pain	1	0	1
Rash	1	0	1
Respiratory disorder	1	0	1
Sinusitis	1	0	1
Vertigo	1	0	1
Total line listings	75	10	85
Total individual events#	50 (6.6%)	8 (4.2%)	58 (6.1%)

*at least one AE in this group was attributed by the investigator to be related to vaccination, all were randomized to receive Fluarix.
Multiple line listings were reported for a single subject experiencing an event. For example, subject number 810 experienced headache, diarrhea, vomiting, pain, and pyrexia 10 days after receiving Fluarix, which could be considered to represent a single adverse event. There were also several reports of subjects experiencing nausea and diarrhea.

Reviewer Comment: grade 3 unsolicited adverse events were infrequent and essentially very similar the rates as reported by the applicant.

Table 8.1.31 Proportion of subjects by study site that did not contain specific data on solicited adverse event (data entry of a ".")

Solicited Adverse event	Study sites			
	11536	11537	11566	11593
Local pain	15 (5.4%)	13 (5.7%)	19 (7.2%)	21 (11.4%)
Headache	66 (23.7%)	58 (25.8%)	57 (21.6%)	22 (11.9%)
Muscle ache	59 (21.2%)	42 (18.7%)	45 (17.0%)	47 (25.4%)

Reviewer comment: Only one study subject had confirmed "missing data" from the recording of solicited adverse events. This analysis of the data was to evaluate whether large discrepancies existed among the study sites in the way that data were recorded and entered. Three solicited local adverse events were selected and evaluated to the occurrence of "." instead of placement of a numerical value (0, 1, 2, or 3) for the recoding of the reactogenicity assessment. No discrepancies in data entry were observed in the datasets submitted to the BLA. The safety data appear to have integrity for purposes of inclusion in product labeling.

The following table summarizes the individual subject case report forms were requested for submission to the BLA because of the potential for violations in study enrollment, such as enrollment of a subject with pre-existing asthma, or severity and characterization of an adverse event.

Table 8.1.32: Requested case report forms

PID	AE	Intensity	Outcome	Causal relationship assessed by investigator
536	Cardiovascular	Met SAE	Death	No
78	Hypothyroidism	Mild	Not resolved	No
803	Rash	Moderate	Not resolved	Yes
426	Angoineurotic edema/ urticaria	Moderate	Resolved	Yes
887	Hypersensitivity	Moderate	Resolved	No
40	Asthma	Not reported AE		
202	Asthma	Not reported AE		

Review of case report forms:
Subject number 202 is a 40 year old Caucasian female who was stated to meet subject eligibility criteria by inclusion/exclusion criteria on the case report form. However, the general medical history form documents "asthma" as a pre-existing condition that was characterized as both past and current. She had never received influenza vaccination. She recorded grade 1 pain, grade 1 shivering, and grade 1 headache on her diary card. She did not experience an unsolicited adverse event during the course of the study. She began use of albuterol unit dose inhaler in 1998 and continued using the inhaler during the study period. No other medicine was administered during the study period.
Reviewer Comment: Although she met criteria for exclusion from the study, she appears to have been under adequate control for her asthma with the use of one inhaled beta-agonist bronchodilator medication. With regular use of an inhaled bronchodilator, asthmatics might be considered to be otherwise healthy volunteers.

Subject number 40 is a 42 year old Caucasian male who had a history of "mild asthma" both past and current with less than three episodes per year. He had not received influenza vaccine in the previous three years. He experienced grade 2 fatigue and headache and grade 1 muscle aches on the day of vaccination. The subject did not use other medications and did not experience an unsolicited adverse event during the study.
Reviewer Comment: As with the subject above, this subject could be considered to be an otherwise healthy volunteer.

Subject number 426 is a 21 year old Caucasian female with a medical history of depression. She had received influenza vaccine on two occasions in the previous three years. She experienced grade 1 pain and grade 2 headache and fatigue on the days following vaccination. Her medications included depoprovera, buproprion, cetirizine, and ibuprofen. She experienced an unsolicited adverse event of moderate hives two days after receipt of the study vaccine. The

hives with "swollen eyes and lips" resolved within 24 hours and the subject did not seek medical attention for the event. The adverse event was moderate and judged to be related to vaccination.

Subject number 78 is a 58 year old Caucasian male who reported a history of prostatic hypertrophy since 1990, for which he received tamsulosin. In addition, he received influenza vaccine in the 2001-2002 year. He experienced mild redness for one day at the site of injection as his only solicited adverse event. Approximately seven days following administration of the study vaccine he began taking thyroid replacement therapy for a new diagnosis of hypothyroidism. The study investigator recorded the event as not related to study vaccine and there are no further data about this adverse event in the case report form.
Reviewer comment: this is a rather unusual presentation to enroll in a study without symptoms and then have a diagnosis of hypothyroidism established just several days after administration of the vaccine. In all likelihood, the hypothyroidism was a sub-clinical pre-existing condition for him at the time of vaccination. It is entirely possible that vaccination enhanced his symptoms. It is also curious that no other solicited adverse event was recorded for this individual that might be attributable to hypothyroidism, such as fatigue. There were no other signals in the safety dataset that might be attributable to hypothyroidism.

Subject 803 is a 19 year old Caucasian female who reported a medical history significant for pneumonia in the past, as well as migraine and allergies to mold and dust mites. She had received influenza vaccine on two occasions in the past three years. She recorded mild pain at the injection site for two days following vaccination. She experienced a generalized rash on the day following vaccination and received pimecrolimus cream 1% and diphenhydramine. The case report form did not describe the date of resolution of the adverse event, but she stopped taking diphenhydramine 10 days after the onset of the rash. She also experienced headache for which she took ibuprofen approximately 2 weeks following vaccination.

Subject 887 is a 25 year old Asian male who reported a medical history of mild seasonal allergies and allergy to cats. He recorded mild pain and arthralgias following vaccination. Approximately 14 days after receipt of study vaccine, he began taking diphenhydramine for an allergic reaction to cats.

The applicant provided a summary of all grade 3 solicited and unsolicited adverse events:

Table 8.1.33 Number, rate, and nature of symptoms (solicited and unsolicited) reported during the 3 day follow-up period and overall (Total Vaccinated Cohort)

	Symptoms					General					Local				
	N	n	%	95% CI of rate		N	n	%	95% CI of rate		N	n	%	95% CI of rate	
				LL	UL				LL	UL				LL	UL
Fluarix	760	540	71.1	67.7	74.3	760	347	45.7	42.1	49.3	760	460	60.5	57.0	64.0
Placebo	192	97	50.5	43.2	57.8	192	77	40.1	33.1	47.4	192	48	25.0	19.0	31.7

Table 8.1.34 Number, rate, and nature of grade 3 symptoms (solicited and unsolicited) reported during the 3 day follow-up period and overall (Total Vaccinated Cohort)

	Symptoms					General					Local				
	N	n	%	95% CI of rate		N	n	%	95% CI of rate		N	n	%	95% CI of rate	
				LL	UL				LL	UL				LL	UL
Fluarix	760	9	1.2	0.5	2.2	760	8	1.1	0.5	2.1	760	2	0.3	0.0	0.9
Placebo	192	5	2.6	0.9	6.0	192	5	2.6	0.9	6.0	192	0	0.0	0.0	1.9

There were no pregnancies reported during the study.

Of the 192 subjects who were randomized to receive placebo, 91 received Fluarix after the subjects were unblinded. Two subjects reported influenza-like illness, both approximately two weeks after receipt of open-label Fluarix in this portion of the study. No other adverse events were reported among this group originally randomized to receive placebo and then received Fluarix.

Comments & Conclusions of Study FluarixUS-001:

- Study FluarixUS-001 was considered to be the "pivotal" clinical trial in this accelerated approval BLA package. The study contained a placebo-control, and data from the study appear to have integrity and were acceptable to support licensure.
- The study met the pre-defined success criteria for proportion with HI antibody titer ≥1:40 and rate of seroconversion. The criteria were based on published clinical data where the proportion with HI antibody titer ≥1:40 of greater than 70% and seroconversion rates greater than 40% are reasonably likely to predict clinical benefit.
- There was one death assumed to be due to cardiovascular disease that occurred during the 21 day follow up period. No other serious adverse events were reported. The solicited local and systemic adverse events were characterized as mild or moderate. Less than 1% of subjects experienced solicited adverse events that were characterized as grade 3 or severe. The rates of symptoms of upper respiratory tract infection, gastrointestinal symptoms, and dysmenorrhea were higher among subjects randomized to receive Fluarix. Most unsolicited adverse events were mild or moderate, with approximately 6% of the unsolicited adverse

events characterized as grade 3 or severe. Approximately 30% of subjects randomized to receive Fluarix did not report an adverse event.

- The safety and efficacy data collected in the study appear to have integrity and are likely to be fully acceptable for review and licensure.
- The study would support the accelerated approval of Fluarix for the prevention of influenza.

8.2 Trial #2: "Open, multicentric, randomized, compared vaccination study (phase IV) to evaluate the non-inferiority of the influenza-vaccine Influsplit SSW®/Fluarix™ 2002/2003 versus the adjuvanted influenza-vaccines Fluad® 2002/2003 and Inflexal V® 2002/2003 concerning immunogenicity and reactogenicity in subjects aged over 60 years."

Applicant's Protocol Number: FLU-052

Objective/Rationale:

- The primary objective was the determination of the non-inferiority of Influsplit SSW®/Fluarix™ 2002/2003 versus 1) Fluad® 2002/2003 and 2) Inflexal V® 2002/2003 in persons over age 60 years as measured by the immunogenicity parameters of Geometric Mean Titers (GMT) of the hemagglutination-inhibition antibodies against the three influenza virus strains represented in the vaccines on day 28 after vaccination. Influsplit SSW®/Fluarix™ 2002/2003 is heretofore identified as Fluarix. Fluad® 2002/2003 (Chiron Behring S.p.A.) and Inflexal V® 2002/2003 (Berna Biotech Ltd.) are heretofore identified as Fluad and Inflexal, respectively. Fluad is a trivalent split subunit vaccine that contains the adjuvant MF-59. Inflexal is a virosome-based trivalent split subunit vaccine. Neither Fluad nor Inflexal is licensed for use in the United States.
- Secondary objectives included the determination of immunogenicity parameters of seroconversion rate and proportion of subjects with HAI titer $\geq$1:40 on day 28 after vaccination. Safety evaluations were also secondary endpoints of the study.

Design Overview:

- The study was a randomized, open-label, active-controlled, multi-center study. Subjects were randomized to receive a 0.5 ml dose of one of the three trivalent influenza vaccines: Fluarix, Fluad, or Inflexal. The study planned to enroll a total of 840 eligible subjects during a recruitment period of 8 weeks in 2002/2003, with 280 subjects per group. Blood sampling was obtained immediately before vaccination and 28 days (+/- 3 days) after vaccination for the primary immune response endpoint. Blood for immunogenicity parameters were obtained at month 4, 8, and 12 after vaccination. Study subjects were monitored for local and systemic adverse events. The study received approval by the Ethics Commission of the Sachsische Landasarztekammer and each of the Ethics Commissions at the study sites.

Population:

- At least 840 subjects greater than 60 years of age were enrolled at 30 study sites in Germany.
- **Inclusion Criteria:**

- Male or female over 60 years of age at the time of vaccination.
- All persons recruited for the study should be not vaccinated with influenza vaccine 2001/2002 and no influenza diseases should be diagnosed in the season 2001/2002.
- Written informed consent obtained from the subject.

- **Exclusion criteria:**
  - Use of any investigational or non-registered drug or vaccine other than the study vaccine within 30 days preceding the vaccination, or planned use during the study period.
  - Acute disease at the time of enrollment. All vaccines can be administered to persons with a minor illness such diarrhea, mild upper respiratory tract infection, with or without low-grade temperature elevation.
  - Acute clinically significant pulmonary, cardiovascular, hepatic, or renal functional abnormality, as determined by physical examination or laboratory screening tests.
  - History of allergic disease or reactions likely to be exacerbated by any component of the vaccine.

Products mandated by the protocol:

- A 0.5 ml dose of trivalent influenza vaccine was administered intramuscularly into the deltoid muscle of the non-dominant arm. The size and length of the 23-gauge needle were identical in all three groups. All three vaccines were commercially available in Germany at the time of the study.

Table 8.2.1 Influenza vaccines used in study FLU-052

Group	Vaccine	Formulation	Lot number
A	Fluarix	0.5 ml pre-filled syringe	18698A9
B	Fluad	0.5 ml pre-filled syringe with needle	3202
C	Inflexal	0.5 pre-filled syringe	3000044

- The vaccines contained HA from three influenza strains for the 2002/2003 year (total HA = 45 µg)
  A/ New Caledonia/20/99 (H1N1)-like strain: 15 µg
  A/Moscow/10/99 (H3N2)-like strain: 15 µg
  B/Hong Kong/330/2001-like strain: 15 µg

Endpoints:

- To show the non-inferiority in terms of immune response after intramuscular administration of the trivalent split influenza vaccine Influsplit SSW®/Fluarix™ 2002/2003 (GlaxoSmithKline/SSW) versus adjuvanted subunit influenza vaccine Fluad® 2002/2003 (Chiron Behring, Chiron S.p.A.) in persons over 60 years measured by the GMTs of the haemagglutination inhibition antibodies against the three influenza virus strains represented in the vaccine post-vaccination.
- To show the non-inferiority in terms of immune response after intramuscular administration of the trivalent split influenza vaccine Influsplit SSW®/ Fluarix™ 2002/2003

(GlaxoSmithKline/SSW) versus the virosome-based subunit influenza vaccine Inflexal V® 2002/2003 (Berna Biotech Ltd.) in persons over 60 years measured by the GMTs of the haemagglutination inhibition antibodies against the three influenza virus strains represented in the vaccine post-vaccination.

- Secondary endpoints included:
  - Descriptive comparison for Fluarix versus Fluad and Fluarix and Inflexarel with regards to seroconversion, defined as a four fold rise in HI antibody titers post-vaccination as compared to baseline, and comparison of proportion of subjects achieving an HI antibody titer equal or greater to 1:40 post vaccination.
  - Descriptive comparisons of reactogenicity and safety including serious adverse events of Fluarix vs. Fluad and Fluarix versus Inflexarel
  - To evaluate the persistence of antibody by follow up at 4, 8, and 12 months after vaccination using analyses of GMT outlined in primary endpoint.

- For purposes of the GMT calculations, subjects with HI antibody titers of less than 1:10 were assigned a value of 1:5.

- Analysis of Primary Immunogenicity Endpoints:

As noted above the co-primary endpoints were to demonstrate 1) the non-inferiority of Fluarix versus Fluad (for each of three strains) and 2) the non-inferiority of Fluarix versus Inflexal (for each of three strains) as measured by assessing the GMT ratios. The global power of the study needed to be at least 90% and the individual power at least of 98% (Bonferroni adjustment of beta for 6 comparisons to take into account the three strains). The non-inferiority of a vaccine is fulfilled, if the non-inferiority for each strain of the vaccine is demonstrated.

The verification of the non-inferiority of the immune response of Fluarix versus Fluad (1st primary endpoint) and Fluarix versus Inflexal V (2nd primary endpoint) was determined for each strain (H1N1, H3N2 and B, three comparisons) by the one(left)-tailed t-test for independent samples:

- one-tailed type I error is set to 0.025 (the global one-tailed alpha will be equal to 0.05 because the study has two primary endpoints)
- comparisonwise type I error rate (PCE) for each strain is 97.5%
- this individual power ensures a global power at least of 90% if the sample sizes are equal to or greater then 262.

The non-inferiority criteria would be fulfilled if the difference of log(GMT) was not greater than 0.176 and the standard deviation is ≤ 0.5. The lower limit of the one-tailed CI of the tested differences of log(GMT) should not include the value 0.176. The limit of non-inferiority is 50% (log of the ratio 1.5).

Reviewer comment: CBER's review focused on retrospective analyses of the rate of seroconversion and percent of subjects achieving an HI antibody titer of equal to or greater than 1:40, assessing the lower bound 95% CI for each of the six endpoints in the Fluarix group to ensure they were above the CHMP criteria. These analyses were in keeping with the pre-defined endpoints for the FluarixUS-001 study and were most relevant because neither Fluad nor Infexal V is approved in the U.S.

Surveillance/Monitoring:

- Demographic data, medical history including influenza vaccination history, blood draw for baseline immune response parameters, and baseline body temperature were performed before vaccination. Subjects were monitored for 15 minutes immediately following vaccination. Subjects recorded temperature and perceived adverse events on a diary card for 3 days, with instructions to call the investigator immediately for any adverse events perceived as serious. Subjects returned at approximately 21-35 days following receipt of vaccine in order to obtain blood draw for immunogenicity parameters, collection and review of diary card, recording of other medications, and recording of adverse events that occurred after vaccination.
- There was no surveillance for influenza infection or symptoms of influenza infection in the study. The study did not have power to detect a difference between the groups in terms of the proportions with clinical disease due to influenza.

- Assessment of reactogenicity variables from the protocol:

  Local solicited symptoms:
  Redness, Induration. Pain
  Intensity: Pain: 0 = nothing reported 1 = mild 2 = moderate 3 = severe
  Redness: 0 = nothing reported 1 = ≤ 20mm 2 = >20 to ≤ 50mm 3 = >50mm diameter
  Induration: 0 = nothing reported 1 = ≤ 20mm 2 = >20 to ≤ 50mm 3 = >50mm diameter
  Intensity:
  all grades of Temperature: 0 = < 37.5°C 1 = 37.5° - 38.0°C 2 = 38.1° - 39.0°C 3 = > 39°C
  all grades of other symptoms.: 0 = nothing reported 1 = mild 2 = moderate 3 = severe

Statistical considerations:

The pre-specified success criterion of non-inferiority of GMTs was a difference not greater than 0.176 (log of ratio 1.5) and the standard deviation is ≤ 0.5 and the lower limit of the one-tailed 97.5% confidence interval should not include the value of 0.176.

- Demographics, analysis of reactogenicity and immunogenicity were performed on the intent to treat cohort.
- Analysis of immunogenicity and reactogenicity were performed on the ATP cohort.
- There were two significant protocol amendments after the protocol was initiated:
  - The post-vaccination period was changed to allow for collection of sera 21-35 days following receipt of vaccine.
  - The lower limit of the age range was 60 years as opposed to 61 years (> 60 years of age).

<u>Results</u> of study FLU-052

Populations enrolled and analyzed:

- The applicant reported that 840 subjects enrolled, but 13 subjects did not receive vaccine. A total of 827 subjects received vaccine. The first subject enrolled October 1, 2002, and the last study visit of the last subject enrolled was January 15, 2003. The ATP cohort consisted of subjects who completed the study period with the data collected as outlined in the table below. The following table describes the subject enrollment and numbers for study analyses.

Table 8.2.2 Subject enrollment and population analyzed for study FLU-052

Subject enrollment	Group			
	Fluarix	Fluad	Inflexal	Total
Number of subjects enrolled	**280**	**280**	**280**	**840**
Subjects not vaccinated	3	4	6	13
Subjects vaccinated	277	276	274	827
Reasons for subject withdrawal				
Diary card missing	2	2	2	6
Drop out	0	1	1	2
Too young	3	0	1	4
Non-compliance	1	0	0	1
Number analyzed immune (ITT)	**277**	**275**	**273**	**825**
Number analyzed immune (ATP)	**273**	**275**	**272**	**820**
Number analyzed reactogenicity (ITT)	**275**	**273**	**271**	**819**
Number analyzed reactogenicity (ATP)	**272**	**273**	**270**	**815**

Approximately 54% of the study subjects were female. About 58% were female in the Fluarix group, 51% in the Fluad group, and 53% in the Inflexal V group. Other demographic characteristics were not provided in the final study report.

The two "drop outs" included one subject who experienced an adverse event that was judged not to be related to vaccination, and one subject voluntarily withdrew consent without providing a reason. Four subjects were enrolled that were below 60 years of age (too young). Six subjects did not return diary cards, two in each treatment group.

Reviewer Comment: CBER requested demographic data with regards to race/ethnicity. The applicant confirmed in a June 30, 2005 BLA amendment that all subjects were Caucasian, except four subjects who were of Asian ethnicity. The applicant did not provide further analysis of the four subjects of Asian ethnicity by treatment group.

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

- Fluarix was determined to be non-inferior to Fluad based on analyses of the primary endpoint of GMT ratio for the A/New Caledonia (HIN1 strain) and the A/Panama (H3N2 strain) but did not meet the non inferiority criteria for the B/Shandong strain. The GMT in the Fluarix group for the B/Shandong strain was 202 (95% CI: 169, 243) and in the Fluad group 273 (95% CI 231, 322). Fluarix was determined to be non-inferior to Inflexal based on analyses of the primary endpoint of GMT to all three strains contained in the vaccine. The following tables describe the seroconversion rates and percent of subjects achieving an HI antibody titer of $\geq$1:40 among subjects randomized to receive Fluarix.

- The applicant's summary of the efficacy data. For purposes of the GMT calculations, subjects with HI antibody titers of less than 1:10 were assigned a value of 1:5.

Table 8.2.3 Secondary endpoint: proportion of subjects (and 95% confidence intervals) with a four-fold rise in HI antibody titers from day 0 to day 21-35, plus subjects with baseline HI antibody titer of less than or equal to 1:10 and achieved a titer of ≥ 1:40 on day 21-35 (seroconversion rate) for subjects randomized to receive Fluarix

Vaccine	N	A/New Caledonia (H1N1) % [95% CI]	A/Panama (H3N2) % [95% CI]	B/Shangdong % [95% CI]
Fluarix	**273**	**78.4 [74, 83]**	**67.0 [61, 73]**	**77.7 [73, 83]**

Table 8.2.4 Secondary endpoint: proportion (and 95% confidence intervals) of subjects with HI antibody titer of ≥ 1:40 on day 21-35 for subjects randomized to receive Fluarix

Vaccine	N	A/New Caledonia (H1N1) % [95% CI]		A/Panama (H3N2) % [95% CI]		B/Shangdong % [95% CI]	
		Day 0	Day 28	Day 0	Day 28	Day 0	Day 28
Fluarix	**273**	**24.5 [19, 30]**	**93.8 [91, 97]**	**33.7 [28, 39]**	**90.1 [87, 94]**	**28.9 [24, 34]**	**91.2 [88, 95]**

Dr. Sang Ahnn provided a post-hoc efficacy analysis of the subgroup 65 years of age or older:

Table 8.2.5 For subjects older than 64 years of age (N=162 out of 273)

Strains	Seroconversion rate [95% CI]	% with HI antibody titer ≥1:40 [95% CI]
H1N1	75.3 [67.9, 81.7]	92.6 [87.4, 96.1]
H3N2	66.1 [58.2, 73.3]	92.0 [86.7, 95.7]
B	74.7 [67.3, 81.2]	93.2 [88.2, 96.6]

Table 8.2.6 The proportion of subjects with baseline HI antibody titers of ≤ 1:10

	A/New Caledonia (H1N1) N (%)	A/Panama (H3N2) N(%)	B/Shangdong N(%)
Fluarix N=273	159 (58.2)	144 (52.7)	137 (50.2)
Fluad N=275	151 (54.9)	141 (51.3)	131 (47.6)
Inflexal N=272	162 (59.6)	142 (52.2)	140 (51.5)

Reviewer Comment: approximately half of the study subjects had baseline HAI titers at or below 1:10.

Reviewer Comment regarding immunogenicity analyses: Using CBER's applied criteria as defined above, all six endpoints were met for entire cohort and those 65 years of age and older who received Fluarix. The sponsor also provided comparative GMT data following day 28, out to month 12 following immunization, but did not provide data on rates of seroconversion and proportion with HI antibody titers ≥1:40 out to month 12.

Safety outcomes:

- Serious Adverse Events: There were four serious adverse events during the study. A 68 year old subject randomized to receive Fluarix experienced angina pectoris 14 days after vaccination. The investigator recorded the recovery from the adverse event. There were no

other serious adverse events in subjects randomized to receive Fluarix. Other serious adverse events that were reported in the study among subjects that received Fluad or Inflexal V include atrial fibrillation, psychotic disorder, and abdominal neoplasm.

- Review of the applicant's summary of unsolicited adverse events:

Table 8.2.7 Unsolicited adverse events study FLU-052

Adverse event category	Fluarix N=273	Fluad N=275	Inflexal V N=272	Total
Upper respiratory tract infection	5	7	5	17
Gastrointestinal	3	3	2	8
Neurological	1	3	2	6
Arthropathy/myalgias	2	0	3	5
Skin- inflammatory	4	0	0	4
Ear-Nose-Throat	0	3	0	3
Other	3	3	2	8
Total	18	19	14	

Table 8.2.8 Solicited local signs and symptoms, highest grade for each subject, all considered to be related to vaccination

	Fluarix			Fluad			Inflexal V		
Symptom	N CBER	N GSK	% [95% CI]	N CBER	N GSK	% [95% CI]	N CBER	N GSK	% [95% CI]
Redness	**39**	**39**	**14.3 [10.1, 18.5]**	**54**	**55**	**20.1 [15.4, 24.8]**	**28**	**29**	**10.7 [7.0, 14.4]**
Grade 1	26	26		36	37		24	25	
Grade 2	12	12		13	13		3	3	
Grade 3	1	1		5	5		1	1	
Pain	**47**	**47**	**17.3 [12.8, 21.8]**	**83**	**83**	**30.4 [25.0, 35.8]**	**47**	**49**	**18.1 [13.5, 22.7]**
Grade 1	39	39		76	76		40	41	
Grade 2	6	6		6	6		7	8	
Grade 3	2	2		1	1		0	0	
Induration	**40**	**40**	**14.7 [10.5, 18.9]**	**56**	**56**	**20.5 [15.7, 25.3]**	**35**	**35**	**13.0 [9.0, 17.0]**
Grade 1	27	27		39	39		30	30	
Grade 2	10	10		13	13		5	5	
Grade 3	3	3		4	4		0	0	

One subject randomized to receive Fluarix experienced redness, pain, and induration for 42 days following vaccination. Eight subjects experienced redness, pain or induration for longer than 3 days, from 4 to 10 days following vaccination.

Reviewer comment: The review of the datasets provided in [redacted] format was nearly entirely consistent with the sponsor's summary table of solicited adverse events. In the few instances where the numbers differed, the applicant's number was always higher, and therefore will accept the proportion of these solicited adverse event data from the applicant. The applicant did not provide the numbers distributed among grade 1, 2, or 3.

Table 8.2.9 Solicited General Symptoms and proportion with grade 3

	Fluarix			Fluad			Inflexal V		
Symptom	N (CBER)	N (GSK)	% [95% CI]	N (CBER)	N (GSK)	%	N (CBER)	N (GSK)	%
Fever	**5**	**5**	**1.8 [0.2, 3.4]**	**3**	**3**	**1.1 [0, 2.3]**	**7**	**7**	**2.6 [0.7, 4.5]**
Grade 3	0			0			0		
Shivering	**13**	**14**	**5.2 [2.6, 7.8]**	**29**	**29**	**10.6 [7.0, 14.2]**	**15**	**14**	**5.2 [2.6, 7.8]**
Grade 3	0			1			0		
Fatigue	**37**	**37**	**13.5 [9.4, 17.6]**	**42**	**42**	**15.3 [11.0, 19.6]**	**32**	**32**	**11.8 [8.0, 15.6]**
Grade 3	1			1			1		
Headache	**43**	**43**	**15.8 [11.5, 20.1]**	**36**	**37**	**13.6 [9.5, 17.7]**	**35**	**35**	**13.0 [9.0, 17.0]**
Grade 3	1			0			1		
Sweating	**11**	**11**	**4.0 [1.7, 6.3]**	**13**	**13**	**4.8 [2.3, 7.3]**	**16**	**16**	**5.9 [3.1, 8.7]**
Grade 3	1			0			0		
Myalgia	**29**	**29**	**10.7 [7.0, 14.4]**	**41**	**41**	**15.0 [10.8, 19.2]**	**26**	**26**	**9.6 [6.1, 13.1]**
Grade 3	2			1			1		
Arthralgia	**25**	**25**	**9.2 [5.8, 12.6]**	**21**	**20**	**7.3 [4.2, 10.4]**	**25**	**25**	**9.3 [5.8, 12.8]**
Grade 3	3			2			1		

Reviewer Comment: The review of the datasets provided in [redacted] format was nearly entirely consistent with the sponsor's summary table of solicited adverse events. In the one instance where the numbers differed for Fluarix group, the applicant's number was higher, and therefore will accept the proportion of these solicited adverse event data from the applicant.

A total of 162 subjects were 65 years of age or older in this study. A review of solicited general symptoms between age groups above and below 65 years of age was conducted in order to ascertain whether an older age group might have different adverse event profile.

Table 8.2.10 Solicited adverse events by age group among subjects randomized to receive Fluarix in study FLU-052

Symptom	Age group 60-64 years N=110		Age group ≥ 65 years N=162	
	N	**% [95% CI]**	**N**	**% [95% CI]**
Redness	**17**	**15.5 [8.7, 22.3]**	**21**	**13.0 [7.8, 18.2]**
Grade 3	0		1	
Pain	**26**	**23.6 [15.7, 31.5]**	**21**	**13.0 [7.8, 18.2]**
Grade 3	0		2	
Induration	**17**	**15.5 [8.7, 22.3]**	**23**	**14.2 [8.8, 19.6]**
Grade 3	1		2	
Fever	**4**	**3.6 [0.1, 7.1]**	**1**	**0.6 [0, 2.5]**
Grade 3	0		0	
Shivering	**4**	**3.6 [0.1, 7.1]**	**9**	**5.6 [2.1, 9.1]**
Grade 3	0		0	
Fatigue	**15**	**13.6 [7.2, 22.0]**	**22**	**13.6 [8.3, 18.9]**
Grade 3	0		1	
Headache	**18**	**16.4 [9.5, 23.3]**	**25**	**15.4 [9.8, 21.0]**
Grade 3	0		1	
Sweating	**4**	**3.6 [0.1, 7.1]**	**7**	**4.3 [1.2, 7.4]**
Grade 3	0		1	
Myalgias	**12**	**10.9 [5.1, 16.7]**	**17**	**10.5 [5.8, 15.2]**
Grade 3	0		2	
Arthralgias	**10**	**9.0 [3.6, 14.4]**	**15**	**9.3 [4.8, 13.8]**
Grade 3	1		2	
Total grade 3	2	1.8 [0, 4.3]	12	7.4 [3.4, 11.4]

Reviewer Comment: There were more grade 3 solicited adverse events among adults age 65 or greater, but the overall rates of adverse events were remarkably similar between the groups.

Comments & Conclusions of Flu-052:

- This study was not designed with a regulatory intent to support licensure of Fluarix. The purpose of the study was to evaluate immune responses and safety responses of Fluarix compared to two other licensed trivalent influenza vaccine products licensed outside the United States. The other influenza vaccine products were purported to have better immune responses and fewer adverse events. Therefore, the applicant's intention of this study was to demonstrate non-inferiority to other licensed vaccine products in Europe.
- The pre-specified success criteria of non-inferiority of Fluarix to the other two vaccines were not met for each of the three antigens. Regardless, the comparisons were made to vaccine products that are not approved in the United States.
- The collection of immune response data, solicited adverse events, and unsolicited adverse events were similar to the collection of these parameters in other studies submitted in this BLA. Therefore, meaningful immune response and safety data were generated from this study in post-hoc analyses.

- The immune response data from the study demonstrate that immune responses likely to predict clinical benefit are observed in the population of adults greater than or equal to 65 years of age. There were no direct comparisons to a younger age group in this study.
- Safety data generated from this study suggest that elderly subjects do not have a different safety profile following administration of Fluarix.

8.3 Trial #3: "Open immunization study to determine the reactogenicity and immunogenicity of Fluarix™/Influsplit SSW®2002/2003 in persons 18 years of age or older."

Applicant's Protocol Number: FLU-051

Objective/Rationale:

- The study FLU-051 was conducted for purposes of yearly registration of influenza vaccine in Europe, which is required by the EMEA when WHO recommends strain changes to the composition of the vaccine from that administered in the previous year. CBER requested that the sponsor submit the study report to the BLA in order to provide additional safety and immunogenicity data in an adult population. The study results would enhance the supportive data to be included in a licensing application.

Design Overview:

- The study was an open-label, non-controlled, non-randomized multicenter study. Each subject, stratified by age, received a single 45 µg dose of influenza vaccine into the deltoid muscle after having blood drawn for HI antibody titer. Study subjects returned 21 days later +/- 3 days for blood draw for HI antibody titer.

Population:

- The study planned to enroll at least 50 adults between 18 and 60 years of age and at least 50 adults over 60 years of age.

Inclusion Criteria:

- Healthy persons and persons with underlying diseases to whom a vaccination against influenza was not contraindicated (cardiovascular disease, respiratory disease, and metabolic disease like diabetes mellitus) as of 18 years of age, who are able to be vaccinated against influenza, and to whom an indication for immunization is obviously seen by the physician.
- Persons who were not immunized against influenza in the previous year and who has no evidence of an influenza disease during the season 2001/2002.
- Informed consent in writing must exist, after clarification of the test persons about the study in an understandable language.

Exclusion Criteria:

- Influenza or other acute infections of the respiratory tract.
- Prodromes of an infectious disease

- Acute feverish disease.
- Allergy against one or more components of the vaccine.
- Gestation.
- Diseases with notable severity (progressive trend of neurological diseases).
- Participation in another study at the same time.
- Other vaccination or immunization at the same time.
- Anamnesis of undesirable or serious undesirable effects after application of influenza vaccines.
- Immunosuppressive medication.

Products mandated by the protocol:

- A 0.5 ml dose of Fluarix was administered to the non-dominant arm in the study. The vaccine contained HA from three influenza strains (total HA = 45 µg) for the 2002/2003 season:

  A/ New Caledonia/20/99 (H1N1)-like strain: 15 µg
  A/Moscow/10/99 (H3N2)-like strain: 15 µg
  B/Hong Kong/330/2001-like strain: 15 µg

  Fluarix contained the following excipients: sodium chloride, [redacted] alpha-tocopheryl hydrogen succinate, polysorbate 80 (Tween 80), octoxynol 9 (Triton X-100), and water. Fluarix was preservative-free, but contains residual levels of thimerosal from early stages of manufacturing, maximum thimerosal content was 0.0025 mg per dose. The lot number used in this trial was Fluarix: Lot #: 18698A9. A 25 gauge needle in a pre-filled syringe was used for all vaccinations.

Endpoints

- Reactogenicity endpoints were determined from diary cards and voluntary information about adverse events at the day 21 study visit.
- Immunogenicity endpoints were collected just prior to the vaccination and at 21 +/- 3 days after vaccination. The primary endpoint was the humoral immune response after intramuscular administration by the day 21 GMT of the HI antibody titer of each of the three antigens. The co-primary endpoint was the description of solicited adverse events.
- Secondary endpoints included the seroconversion rate and the proportion with HI antibody titers ≥1:40 on day 21 of vaccination.
- Serious adverse events collected during the trial.

Reviewer Comment: The endpoints appear to be appropriate and were designed to address the CHMP criteria for yearly licensure of inactivated influenza vaccine in the European Union. The use of HI antibody titer has a reasonable likelihood of predicting clinical benefit of the vaccination.

Surveillance/Monitoring:

- Demographic data, medical history including influenza vaccination history, directed physical examination "if deemed necessary", urine pregnancy test if female, blood draw for baseline immune response parameters, and baseline body temperature were performed before vaccination. Subjects were monitored for 15 to 30 minutes immediately following vaccination. Subjects recorded temperature and perceived adverse events on a diary card for 3 days, with instructions to call the investigator immediately for any adverse events perceived as serious. Subjects returned at approximately 21 days following receipt of vaccine in order to obtain blood draw for immunogenicity parameters, collection and review of diary card, recording of other medications, and recording of unsolicited symptoms that may have occurred after vaccination. There was no surveillance for influenza infection or symptoms of influenza infection in the study.

Table 8.3.1 Intensity scales for solicited symptoms in adults

Adverse event	Intensity grade	Parameter
Pain at injection site, headache, fatigue, joint pain (arthralgias), muscle ache (myalgias), shivering	0	Absent
	1	Is easily tolerated
	2	Interferes with normal activity
	3	Prevents normal activity
Redness/swelling at injection site	0	0 mm
	1	> 0 - ≤ 20 mm
	2	> 20 - ≤ 50 mm
	3	> 50 mm
Fever	0	< 37.5ºC
	1	≥ 37.5 - ≤ 38.0ºC
	2	> 38.0 – 39.0ºC
	3	> 39.0ºC

Comment: the same intensity scale was used for FluarixUS-001 study.

Statistical considerations:

- The applicant defined the primary endpoint as the GMT before and 21 days after vaccination. The applicant evaluated the immunogenicity parameters as per the European Union recommendations for yearly evaluation of influenza vaccines, which are described in section "Endpoints".

Reviewer Comment: the sponsor chose the GMT as the primary endpoint, without any of the three components of the CHMP criteria for immune response: CHMP seroconversion factor, CHMP seroconversion rate, and proportion with HI antibody titer ≥1:40.

Results, study FLU-051:

Populations enrolled and analyzed:

- Applicant's analysis: Eight clinical trial sites in Dresden, Germany enrolled 120 subjects, but only 114 received vaccine. A total of 59 subjects were between 18 and 60 years with a mean age of 35.1 years and approximately 64% were female. A total of 56 subjects were over 60 years of age with a mean age of 70.3 years and approximately 71% were female. The study began on May 27, 2002 and the study was completed June 21, 2002. The applicant reported that all study subjects were Caucasian.

Table 8.3.2 Underlying medical conditions summarized by the applicant

Age group	Age group	
Medical condition category	18-60 N=59	> 60 N=55
Nothing reported	23 (38%)	3 (5%)
Respiratory tract	6 (10%)	10/55 (18%)
Cardiovascular	15 (25%)	39 (71%)
Metabolic/endocrine	12 (20%)	22 (40%)

- Reviewers analysis: Of the 114 study subjects for which demographic information was available on datasets submitted to the BLA, 55 subjects were over 60 years of age and 59 subjects were between 18 and 65 years of age. Of the subjects 18 to 60 years of age, 64% were female with a median age of 35 years. Of the subjects over 60 years, 71% were female with a median age of 67 years.

Efficacy endpoints and outcomes, summary of applicant's analyses

The sponsor provided the immunological endpoints, point estimates with 95% confidence intervals, in the table below:

Table 8.3.3 Immunological endpoints study FLU-O51

		18 – 60 years (n=58)	EU	>60 years (n=54)	EU
Sero-conversion rate	H1N1 H3N2 B	83 [71 – 91]% 69 [56 – 81]% 85 [73 – 93]%	> 40 %	59 [45 – 72]% 56 [41 – 69]% 59 [45 – 72] %	> 30 %
GMT increase	H1N1 H3N2 B	24,0 [15,5 – 37,3] 7,9 [5,3 – 11,8] 12,5 [9,3 – 16,9]	> 2,5	8,4 [5,5 – 12,8] 6,1 [4,0 –9,2] 8,0 [5,2 – 12,1]	> 2,0
% with HI antibody titer ≥1:40	H1N1 H3N2 B	98 [91 – 100] % 98 [91 – 100]% 98 [91 – 100] %	> 70 %	94 [85 –99]% 94 [85 –99]% 94 [85 -99]%	> 60 %

FDA review: Dr. Sang Ahnn provided the immunogenicity parameters of seroconversion rate and proportion with HI antibody titers ≥1:40 for subjects ≥ 65 years of age:

Table 8.3.4 Immunological endpoints in subjects older than 64 years of age (N=38 out of 112)

Strains	Seroconversion rate	% with HI antibody titer ≥1:40
H1N1	55.3 (38.3, 71.4)	97.4 (86.2, 99.9)
H3N2	50.0 (33.4, 66.6)	94.7 (82.3, 99.4)
B	60.5 (43.4, 76.0)	97.4 (86.2, 99.9)

Reviewer comment:
The point estimates and the lower bound of the 95% confidence intervals are above the CHMP criteria for > 60 years of age for all three antigens. When comparing to the CHMP criteria for the age group below 60 years of age, the lower bound of the 95% confidence interval for proportion with HI antibody titers ≥1:40 and seroconversion met success criteria for the B antigen and the lower bound of the 95% confidence intervals for proportion with HI antibody titers ≥1:40 for the A antigens met success criteria. When applying the applicant's original pre-specified success criteria of point estimates of 55.4% seroconversion and 87.5% with HI antibody titers ≥1:40, the point estimates of seroconversion rate for the A antigen strains did not meet the success criteria and the point estimate of seroconversion rate for the B antigen met success criteria. The 95% confidence intervals are large due to the small sample size of this subgroup. The proportion with HI antibody titers ≥1:40 all met success criteria by point

estimates. The lower bound of the 95% confidence interval just surpassed 87.5% for the H1N1 strain and the B strain.

Safety outcomes:

Review of the applicant's summary adverse events:
Serious Adverse Events:
One serious adverse event was reported during the study and the case report form was provided in the BLA. Subject number 1016 is a 55 year old Caucasian man who did not experience local or systemic reactions but experienced a peritonsillar abscess seven days following vaccination. He recovered with antibiotic therapy and the event was judged by the investigator to be not related to vaccination. Seven subjects reported unsolicited adverse events during the 21 day trial. Two subjects experienced rhinitis, four subjects experienced conjunctivitis, facial flushing, viral infection, and vertigo. The investigator attributed the facial flushing to the administration of Fluarix. The adverse event of facial flushing occurred on May 30, 2002, and lasted one day. The study began on May 27, 2002. Therefore, the facial flushing occurred within 3 days following vaccination with Fluarix. The seventh subject experienced cardiovascular disorder that was not labeled a serous adverse event and case report form was not submitted with the BLA. The investigator did not attribute the adverse event to vaccination.

Table 8.3.5 Sponsor table of solicited adverse events from final study report

			adults		elderly	
Reported symptoms in the period from day of vaccination to 3rd day after vacc.			age group 18-60 yrs		age group > 60 yrs	
			n= 59		n= 55	
			n	%	n	%
Local reactions						
		intensity 1	9	15,3	5	9,1
	Redness	intensity 2	4	6,8	5	9,1
		intensity 3	2	3,4	2	3,6
		total:	15	25,4	12	21,8
		intensity 1	17	28,8	7	12,7
	Pain	intensity 2	9	15,3	3	5,5
		intensity 3	0	0,0	0	0,0
		total:	26	44,1	10	18,2
		intensity 1	12	20,3	13	23,6
	Induration	intensity 2	2	3,4	3	5,5
		intensity 3	1	1,7	1	1,8
		total:	15	25,4	17	30,9
Systemic reactions	**Exclusion of all symptoms not related to vaccination**					
		intensity 1	1	1,7	0	0,0
	Fever	intensity 2	0	0,0	0	0,0
		intensity 3	0	0,0	0	0,0
		total:	1	1,7	0	0,0
		intensity 1	2	3,4	5	9,1
	Shivering	intensity 2	1	1,7	0	0,0
		intensity 3	0	0,0	0	0,0
		total:	3	5,1	5	9,1
		intensity 1	7	11,9	3	5,5
	Fatique	intensity 2	2	3,4	3	5,5
		intensity 3	0	0,0	0	0,0
		total:	9	15,3	6	10,9
		intensity 1	4	6,8	2	3,6
	Headache	intensity 2	4	6,8	0	0,0
		intensity 3	0	0,0	0	0,0
		total:	8	13,6	2	3,6
		intensity 1	2	3,4	2	3,6
	Sweating	intensity 2	1	1,7	0	0,0
		intensity 3	0	0,0	0	0,0
		total:	3	5,1	2	3,6
		intensity 1	8	13,6	3	5,5
	Myalgia	intensity 2	2	3,4	1	1,8
		intensity 3	0	0,0	0	0,0
		total:	10	16,9	4	7,3
		intensity 1	1	1,7	3	5,5
	Arthralgia	intensity 2	4	6,8	1	1,8
		intensity 3	0	0,0	0	0,0
		total:	5	8,5	4	7,3
		definitions of symptoms intensity 1, 2, 3 see protocol				

Reviewer Comment: The sponsor excluded solicited adverse events that were judged to be unrelated to vaccination.

Medical Officer's review of solicited adverse events by age group above and below 65 years of age, percentage of subjects experiencing adverse event, highest rated by grade per subject and 95% confidence interval.

Table 8.3.5 Solicited adverse events

	Age category			
	18-64 years n=75		≥65 years n=39	
Solicited AE	**N**	**% [95% CI]**	**N**	**% [95% CI]**
Induration	**21**	**28.0 [17.8, 38.2]**	**11**	**28.2 [14.1, 43.3]**
Grade 1	17		8	
Grade 2	3		2	
Grade 3	1		1	
Fever	**2**	**2.7 [0, 7.8]**	**0**	**0 [0, 3.1]**
Grade 1	2		0	
Grade 2	0		0	
Grade 3	0		0	
Shivering	**3**	**4.0 [0, 8.4]**	**6**	**15.4 [4.1, 26.7]**
Grade 1	2		5	
Grade 2	1		1	
Grade 3	0		0	
Fatigue	**18**	**24.0 [14.3, 33.7]**	**6**	**15.4 [4.1, 26.7]**
Grade 1	14		4	
Grade 2	3		2	
Grade 3	1		0	
Headache	**12**	**16.0 [7.7, 23.7]**	**7**	**17.9 [5.9, 29.9]**
Grade 1	6		7	
Grade 2	6		0	
Grade 3	0		0	
Sweating	**4**	**5.3 [0.2, 10.4]**	**4**	**10.3 [0.8, 19.8]**
Grade 1	2		4	
Grade 2	1		0	
Grade 3	1		0	
Myalgias	**14**	**18.7 [9.9, 27.5]**	**4**	**10.3 [0.8, 19.8]**
Grade 1	10		3	
Grade 2	4		1	
Grade 3	0		0	
Arthralgias	**7**	**9.3 [2.7, 15.9]**	**5**	**12.8 [2.3, 23.3]**
Grade 1	2		3	
Grade 2	5		2	
Grade 3	0		0	

Comments & Conclusions:

- This study was not designed with a regulatory intent to support U.S. licensure of Fluarix. The purpose of the study was to evaluate immune responses and safety responses of Fluarix for the trivalent formulation for the 2002-2003 year. This study is a requirement for maintenance of licensure in countries in the European Union.
- The collection of immune response data, solicited adverse events, and unsolicited adverse events were similar to the collection of these parameters in other studies submitted in this BLA. Therefore, meaningful immune response and safety data were generated from this study in post-hoc analyses.
- The immune response data from the study demonstrate that sufficient immune responses are observed in the population of adults greater than or equal to 65 years of age. There were no direct comparisons to a younger age group in this study.
- Safety data generated from this study suggest that elderly subjects do not have a different safety profile following administration of Fluarix.

8.4 **Trial #4:** "Open immunization study to determine the reactogenicity and immunogenicity of Fluarix™/Influsplit SSW®2004/2005 in persons as of 18 years of age."

Applicant's Protocol Number: FLU-058

Objective/Rationale:

- The study was conducted for purposes of yearly registration of influenza vaccine in Europe, which is required by the EMEA when WHO recommends strain changes to the composition of the vaccine from that administered in the previous year. CBER requested that the sponsor submit the study report to the BLA in order to provide additional safety and immunogenicity data in an adult population. The study results would enhance the supportive data to be included in a licensing application.

Design Overview:

- The study was an open-label, non-controlled, non-randomized multicenter study. Each subject received a single 45 μg dose of 2004/2005 influenza vaccine into the deltoid muscle after having blood drawn for HI antibody titer. Study subjects returned 21 days later for blood draw for HI antibody titer, as well as the collection of local, systemic, and unsolicited adverse events.

Population:

- The study planned to enroll approximately 60 adults between 18 and 60 years of age and 60 adults over 60 years of age.

Inclusion Criteria:

- A male or female aged 18 years at the time of vaccination, not vaccinated against influenza in the previous season.
- Written informed consent obtained from the subject.

Exclusion Criteria:

- Use of any investigational or non-registered drug or vaccine other than the study vaccine within 30 days preceding the vaccination, or planned use during the study period.
- Acute disease at the time of enrollment. All vaccines can be administered to persons with minor illness such as diarrhea, mild upper respiratory tract infection with or without low-grade febrile illness, i.e., oral/axillary temperature < 37.5°C.
- Acute clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests.
- Pregnant female.
- Female who is willing to become pregnant during the period starting the day of vaccination and ending one month after vaccination.
- History of allergic disease or reactions likely to be exacerbated by any component of the vaccine.

Products mandated by the protocol:

- A 0.5 ml dose of Fluarix was administered to the non-dominant arm in the study. The vaccine contained HA from three influenza strains (total HA = 45 µg) for the 2004/2005 season:

  A/ New Caledonia/20/99 (H1N1)-like strain: 15 µg
  A/Fujian/411/2002 (H3N2)-like strain: 15 µg
  B/Shangai/361/2002-like strain: 15 µg

  Fluarix contained the following excipients: sodium chloride, [redacted] alpha-tocopheryl hydrogen succinate, polysorbate 80 (Tween 80), octoxynol 9 (Triton X-100), and water. Fluarix was preservative-free, but contains residual levels of thimerosal from early stages of manufacturing; maximum thimerosal content was 0.0025 mg per dose. The lot number used in this trial was Fluarix: Lot # AFLUA015A. A 25 gauge needle was used for all vaccinations.

Endpoints:

- The primary endpoint was the humoral immune response after intramuscular administration by the day 21 GMT of the HI antibody titer of each of the three antigens. The co-primary endpoint was the description of solicited adverse events.
- Secondary endpoints included the seroconversion rate and the proportion with HI antibody titer ≥1:40 on day 21 vaccination.
- Serious adverse events collected during the trial.

Comment: The endpoints appear to be appropriate for the original purpose of the study. A 2003/2004 study did not take place because the vaccine strain recommendation by the WHO remained the same and therefore new antigens were not going to be included in the vaccine for that year. The use of HI antibody titer has a reasonable likelihood of predicting clinical benefit of the vaccination.

Surveillance/Monitoring:

- Demographic data, medical history including influenza vaccination history, directed physical examination "if deemed necessary", urine pregnancy test if female, blood draw for baseline immune response parameters, and baseline body temperature were performed before vaccination. Subjects were monitored for 15 to 30 minutes immediately following vaccination. Subjects recorded temperature and perceived adverse events on a diary card for 3 days, with instructions to call the investigator immediately for any adverse events perceived as serious. Subjects returned at approximately 21 days (+/- 2 days) following receipt of vaccine in order to obtain blood draw for immunogenicity parameters, collection and review of diary card, recording of other medications, and recording of unsolicited symptoms that may have occurred after vaccination. Telephone interview occurred at day 30 in order to collect information on adverse events that may have occurred following the day 21 study visit. There was no surveillance for influenza infection or symptoms of influenza infection in the study.

Table 8.4.1 Intensity scales for solicited symptoms in adults

Adverse event	Intensity grade	Parameter
Pain at injection site, headache, fatigue, joint pain (arthralgia), muscle ache (myalgia), shivering	0	Absent
	1	Is easily tolerated
	2	Interferes with normal activity
	3	Prevents normal activity
Redness/swelling at injection site	0	0 mm
	1	> 0 - ≤ 20 mm
	2	> 20 - ≤ 50 mm
	3	> 50 mm
Fever	0	< 37.5ºC
	1	≥ 37.5 - ≤ 38.0ºC
	2	> 38.0 – 39.0ºC
	3	> 39.0ºC

Reviewer comment: this study used the same intensity scale for FluarixUS-001 study and the other studies in this BLA.

Statistical considerations:

- The applicant defined the primary endpoint and statistical analyses as per recommendations of the EMEA CHMP criteria for yearly strain changes. The HI antibody titers were analyzed by seroconversion rate, seroconversion factor, and proportion with HI antibody titers ≥1:40. See table 5.2 for a description of the CHMP criteria.

Results, study FLU-058

Populations enrolled and analyzed

- Sponsor's analysis: Four clinical trials sites in Dresden, Germany enrolled 120 subjects. A total of 64 subjects were between 18-60 years with a mean age of 38.94 years and approximately 50% were female. A total of 56 subjects were over 60 years of age with a mean age of 69.13 years and approximately 63% were female. The study began on June 28, 2004 and the data lock point was July 30, 2004, approximately 30 days after the last person enrolled in the study received vaccine.

Table 8.4.2 Numbers of subjects enrolled by study site

Investigator	18-60 years	> 60 years	Total
Reiners, B	20	20	40
Elefant, G	8	8	16
Reimer, N	22	18	40
Bohme, M	14	10	24
Total	64	56	120

- The sponsor reports that no subjects withdrew from the study and that all study subjects were eligible for inclusion in the immunogenicity and reactogenicity assessments. Four study subjects were enrolled and initially placed into the incorrect age group of > 60 years; the four subjects were analyzed in the 18-60 year age group. The sponsor reported that all study subjects returned the 3 day diary card.

Comment: The enrollment appears to be equally distributed at each study center. The sponsor did not provide additional demographic characteristics in the original BLA, but stated in a June 30, 2005 amendment that one subject in the study was of African decent while the remainder of study subjects were Caucasian.

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

- The applicant provided the following summary of the HI antibody results:

Table 8.4.3 Geometric mean titer (and 95% confidence intervals) pre and 21 day post vaccination

Age group	N	day 0			day 21		
		A/New-Caledonia (H1N1)	A/ A/Wyoming (H3N2)	B/ Jiangsu	A/New-Caledonia (H1N1)	A/ A/Wyoming (H3N2)	B/ Jiangsu
		GMT [95% CI]	GMT [95% CI]	GMT [95% CI]	GMT [95% CI]	GMT [95% CI]	GMT [95% CI]
18 – 60 years	64	32 [21 – 49]	48 [33 – 70]	23 [17 –32]	381 [270 –536]	600 [457 –787]	292 [226 –376]
> 60 years	56	20 [14 – 28]	27 [18 – 39]	21 [15 –29]	139 [101 –190]	473 [319 – 700]	223 [170 -293]

Table 8.4.4 Seroconversion rate (and 95% confidence intervals) pre- to post-vaccination

Age group	N	Criteria of CHMP	A/New-Caledonia (H1N1) [95% CI]	A/Wyoming (H31N2) [95% CI]	B/Jiangsu [95% CI]
18 – 60 years	64	>40%	64.1 [52 – 76]	73.4 [63 – 84]	78.1 [68 – 88]
> 60 years	56	>30%	55.4 [42 – 68]	78.6 [68 – 89]	76.8 [66 – 88]

Table 8.4.5 Proportion with HI antibody titers ≥1:40 (and 95% confidence intervals) at 21 days post-vaccination

Age group	N	Criteria of CHMP	A/New-Caledonia (H1N1) [95% CI]	A/Wyoming (H31N2) [95% CI]	B/Jiangsu [95% CI]
18 – 60 years	64	>70%	95.3 [88 – 99]	100.0 [95 – 100]	96.9 [90 – 99]
> 60 years	56	>60%	87.5 [77 – 94]	94.6 [86 – 99]	94.6 [86 – 99]

Reviewer Comment: The lower bounds of the 95% confidence intervals for seroconversion and proportion of subjects with HI antibody titers ≥1:40 exceeded the criteria set forth by the CHMP for each of the three antigens. When applying the CHMP criteria for the age group 18-60 years, the lower bound of the 95% confidence intervals for seroconversion rate and proportion with HI antibody titers ≥1:40 in the > 60 years age group exceeded the CHMP criteria for each of the three antigens.

The following represents a summary of Dr. Sang Ahnn's summary of the statistical review of the efficacy endpoints:

Table 8.4.6 FLU-058 For subjects older than 64 years of age (N=46 out of 120)

Strains	Seroconversion rate	% with HI antibody titers ≥1:40
H1N1	54.4 (39.0, 69.1)	87.0 (73.7, 95.1)
H3N2	82.6 (68.6, 92.2)	93.5 (82.1, 98.6)
B	78.3 (63.6, 89.1)	95.7 (85.2, 99.5)

Comments: For this post-hoc analysis of seroconversion rate and proportion with HI antibody titers ≥1:40, the lower bound of the 95% confidence interval exceeded the CHMP criteria for the > 60 age group for all three antigens. When applying the CHMP criteria for the age group 18-60 years, only seroconversion rate for the A/New Caledonia H1N1 fell below the CHMP criteria, while the lower bounds of the 95% confidence interval exceeded the criteria for the other five endpoints. The point estimates for this subgroup analysis exceeded the applicant's definition of "worst case scenario" of seroconversion of 55.4% and proportion with HI antibody titer ≥1:40 of 87.5%. However, for the H1N1 strain, where the seroconversion rate was 54.4% and the proportion with HI antibody titer ≥1:40 was 87.0%, this was nearly identical to the applicant's definition of "worst case scenario".

Safety outcomes:

Review of the applicant's summary adverse events:
Serious Adverse Events: There were no serious adverse events reported in the study.
Unsolicited adverse events: Two subjects reported unsolicited adverse events during the study that were judged by the investigator to be related to vaccination. One subject experienced chills for one day on the day following vaccination. Another subject experienced erythema and itching that occurred one day following vaccination. The remaining six subjects with unsolicited adverse events were judged by the investigator to be unrelated to vaccination. Four subjects experienced mild upper respiratory tract symptoms, such as rhinitis, sore throat, and headache. One subject experienced myalgias five days after vaccination and another subject experienced tendonitis eight days after vaccination that was determined by the investigator to be not related to vaccination.

Comments: None of the unsolicited adverse events appear to be unusual or generate concern of a potential safety signal.

Table 8.4.7 Applicant's summary of solicited adverse events provided in tabular format

Symptoms	Level*	18-60 years All	18-60 years (N=64) %	> 60 years All	> 60 years (N=56) %
Redness (total)		19	29.7	15	26.8
	grade 1	7	10.9	5	8.9
	grade 2	8	12.5	4	7.1
	grade 3	4	6.3	6	10.7
Pain (total)		37	57.8	7	12.5
	grade 1	28	43.8	6	10.7
	grade 2	8	12.5	1	1.8
	grade 3	1	1.6	0	0
Induration (total)		23	35.9	9	16.1
	grade 1	18	28.1	4	7.1
	grade 2	3	4.7	3	5.4
	grade 3	2	3.1	2	3.6

Table 8.4.8 Systemic solicited adverse events judged to be related to vaccination by the investigator

Symptoms*	Relationship	18-60 years (N=64) All	%	>60 years (N=56) All	%
Fever >37.5° C	All	0	0	0	0
	related**	0	0	0	0
	not related	0	0	0	0
Shivering	All	2	3.2	3	5.4
	related**	1	1.6	0	0
	not related	1	1.6	3	5.4
Fatigue	All	12	18.8	2	3.6
	related**	1	1.6	0	0
	not related	11	17.2	2	3.6
Headache	All	12	18.8	4	7.1
	related**	0	0	0	0
	not related	12	18.8	4	7.1
Sweating	All	6	9.4	5	8.9
	related**	0	0	0	0
	not related	6	9.4	5	8.9
Myalgia	All	12	18.8	6	10.7
	related**	3	4.7	0	0
	not related	9	14.1	6	10.7
Arthralgia	All	4	6.3	7	12.5
	related**	0	0	0	0
	not related	4	6.3	7	12.5

Table 8.4.9 Medical officer review of solicited AE between two age categories

	Age category			
Solicited adverse event	18-64 years n=74		≥ 65 years n=46	
	N	% [95% CI]	N	% [95% CI]
Redness	**22**	**29.7 [19.3, 40.1]**	**12**	**26.1 [13.4, 38.8]**
Grade 1	7		5	
Grade 2	9		3	
Grade 3	6		4	
Pain	**39**	**52.7 [41.3, 64.1]**	**5**	**10.9 [1.9, 19.9]**
Grade 1	30		4	
Grade 2	8		1	
Grade 3	1		0	
Induration	**25**	**33.8 [23.0, 44.6]**	**7**	**15.2 [4.8, 25.6]**
Grade 1	18		4	
Grade 2	4		2	
Grade 3	3		1	
Fever	**0**	**0 [0, 2.3]**	**0**	**0 [0, 2.9]**
Grade 1	0		0	
Grade 2	0		0	
Grade 3	0		0	
Shivering	**2**	**2.7 [0. 6.4]**	**3**	**6.5 [0, 13.6]**
Grade 1	1		3	
Grade 2	1		0	
Grade 3	0		0	
Fatigue	**12**	**16.2 [7.8, 24.6]**	**2**	**4.3 [0, 10.2]**
Grade 1	0		0	
Grade 2	0		0	
Grade 3	0		0	
Headache	**13**	**17.6 [8.9, 26.3]**	**3**	**6.5 [0, 13.6]**
Grade 1	11		3	
Grade 2	2		0	
Grade 3	0		0	
Sweating	**8**	**10.8 [3.7, 17.9]**	**3**	**6.5 [0, 13.6]**
Grade 1	7		3	
Grade 2	1		0	
Grade 3	0		0	
Myalgias	**14**	**18.9 [10.0, 27.8]**	**4**	**8.7 [0.6, 16.8]**
Grade 1	12		3	
Grade 2	2		1	
Grade 3	0		0	
Arthralgias	**4**	**5.4 [0.2, 10.6]**	**7**	**15.2 [4.8, 25.6]**
Grade 1	4		6	
Grade 2	0		1	
Grade 3	0		0	

Comments & Conclusions:

- This study was not designed with a regulatory intent to support U.S. licensure of Fluarix. The purpose of the study was to evaluate immune responses and safety responses of Fluarix for the trivalent formulation for the 2002-2003 year. This study is a requirement for maintenance of licensure in countries in the European Union.
- The collection of immune response data, solicited adverse events, and unsolicited adverse events were similar to the collection of these parameters in other studies submitted in this BLA. Therefore, meaningful immune response and safety data were generated from this study in post-hoc analyses.
- The immune response data from the study demonstrate that sufficient immune responses are observed in the population of adults greater than or equal to 65 years of age. There were no direct comparisons to a younger age group in this study.
- Safety data generated from this study suggest that elderly subjects do not have a different safety profile following administration of Fluarix.

9 Overview of Efficacy Across Trials

- The following table summarizes the efficacy results of the four trials submitted in the BLA. The immunogenicity results from studies Flu-051 and Flu-058 are combined to include all adults that received Fluarix in these studies.

Table 9.1 Point estimates of efficacy endpoints for adult subjects receiving Fluarix in each of the four studies submitted to the BLA

STUDY	ENDPOINT	A/H1N1 %	A/H3N2 %	B %
FluarixUS-001	**Prop. ≥ 1:40**	**96.6**	**99.1**	**98.8**
	Seroconversion	***59.6***	***61.9***	***77.6***
Flu-052	**Prop. ≥ 1:40**	**93.8**	**90.1**	**91.2**
	Seroconversion	***78.4***	***67.0***	***77.7***
Flu-051	**Prop. ≥ 1:40**	**96.4**	**96.4**	**96.4**
	Seroconversion	***71.4***	***63.5***	***72.3***
Flu-058	**Prop. ≥ 1:40**	**91.7**	**97.5**	**95.8**
	Seroconversion	***60.0***	***75.8***	***77.5***

- The studies were conducted at different time periods using Fluarix that contained different antigenic formulations. For each study and for each antigen class, Fluarix generated immune response parameters that were similar across studies.
- For each study, the point estimate for the proportion of subjects with HI antibody titer ≥1:40 and the seroconversion rates were above the criteria established by the EMEA CHMP for each of the three antigens.
- The results of the four clinical trials demonstrate that administration of Fluarix results in sufficient immune response parameters among adults ages 18 and older that are reasonably likely to predict clinical benefit.

10 Overview of Safety Across Trials

- Solicited adverse events for three days following vaccination were collected in a nearly identical and systematic way that enhances the ability to compare across all four trials conducted by GSK.

- **Table 10.1 Percent of subjects reporting solicited adverse events**

	FluarixUS-001	Flu-052	Flu-051	Flu-058
Local Redness	17.5	14.3	23.7	28.3
Local Swelling	9.5	14.7	28.1	26.7
Local pain	55.6	17.3	31.6	36.7
Fatigue	20.1	13.5	13.2	11.7
Headache	19.3	15.8	8.8	13.3
Muscle aches	23.2	10.7	12.3	15.0
Shivering	3.2	*	7.0	4.4
Joint pain	6.1	9.2	7.9	9.2
Fever	1.3	1.8	0.9	0.0
Sweating	*	4.0	4.4	9.2

* Sweating was not included in the diary card for study FluarixUS-001 and shivering was not included in the diary card for study Flu-052.

- The safety data collected as part of the diary card's solicited adverse events were similar for all four studies, where subjects kept records of the local and systemic adverse events for three days following vaccination.
- There were somewhat lower rates of solicited adverse events in study Flu-052, which enrolled subjects greater than 60 years of age. In studies Flu-051 and Flu-058, rates of solicited adverse events were lower in subjects greater than 65 years of age.
- Most of the solicited adverse event rates were characterized as mild or moderate. There were very few severe or grade 3 adverse events.
- Patterns of unsolicited adverse events that emerged among the data collected in the four trials included gastrointestinal symptoms of nausea, vomiting, and diarrhea, symptoms of upper respiratory tract infection, and dysmenorrhea. The proportions of subjects with these unsolicited adverse events were less than 5%. None were characterized as severe.
- A review of the spontaneous adverse event reports that were submitted to IND [redacted] as part of the ongoing IND safety reporting requirements included the adverse events that had not been described in the sponsor's original version of the "POSTMARKETING" section of product labeling. These adverse events included: autoimmune hemolytic anemia, injection site abscess, injection site cellulitis, Henoch-Schonlein purpura, and myelitis.
- Three deaths were recorded among the subjects enrolled in the studies. One subject died from complications of coronary artery disease 17 days after vaccination with Fluarix. One subject died from acute pancreatitis 10 months after vaccination with Fluarix. One subject died from complications of an abdominal neoplasm 9 months after vaccination with Fluarix. There were no clear patterns from the deaths observed in the clinical trials.

- Adverse events that had potential to represent an allergic reaction to administration of Fluarix included two subjects who experienced urticaria and generalized rash in study FluarixUS-001, one subject experienced facial flushing study FLU-051, and one subject experienced erythema and itching in study FLU-058. For all of these adverse events, the investigator judged the adverse events to be related to vaccination with Fluarix. These events were self-limited and were characterized as resolved within several days.
- There were few dropouts in the four studies submitted to the BLA, and therefore the dropouts are not likely to adversely affect the characteristics of the safety profile.

Safety Conclusions

- The safety profile of Fluarix, as presented in the studies submitted to the BLA and in postmarketing reports submitted to the active IND, appears to be well-balanced when considering the potential benefit of influenza vaccination.

11. Dose Regimens and Administration

- Fluarix will be supplied as a single 0.5 mL dose of a colorless suspension in a pre-filled syringe packaged without needles.

12 Special Populations

- The pivotal study FluarixUS-001 enrolled a racially diverse population in the United States, while the other studies used for supportive evidence of safety and immune response characteristics enrolled primarily Caucasian populations.

Geriatrics

- There were sufficient data in the BLA that supported the demonstration of acceptable safety and acceptable immune response parameters when Fluarix was given to an elderly population.

Pediatrics

- The applicant did not submit clinical data that would support the use of Fluarix in the pediatric population. [redacted]. A deferral of the completion of clinical trials to support the use of Fluarix in the pediatric population will be granted at the time of approval.

13 Conclusions - Overall

- The clinical data submitted in this BLA support the safety and efficacy of Fluarix when administered to adults greater than 18 years of age. The efficacy data is based on a surrogate endpoint of immune response parameters of proportion of subjects with HI antibody titers $\geq$1:40 and seroconversion rate following administration of Fluarix. These endpoints are reasonably likely to predict clinical benefit of Fluarix. The safety concerns are primarily mild to moderate local injection site reactions and mild to moderate systemic adverse events, which are usually self-limited.

14 Recommendations

- It is recommended that Fluarix be approved for the indication of active immunization of adults against influenza disease caused by influenza virus types A and B contained in the vaccine.

Recommendations on Postmarketing Actions

- The applicant submitted three draft clinical trials with plans to conduct the studies in order to support the traditional approval of Fluarix.
- Study FluarixUS-003 will be a immunogenicity study of subjects who fall within groups that should receive influenza vaccination and will compare Fluarix to a U.S. licensed vaccine, likely to be Fluzone®.
- Study FluarixUS-004 will be a clinical endpoint efficacy study of Fluarix versus placebo in an adult population for whom vaccination is not universally recommended. The primary endpoint will be culture confirmed influenza illness.
- Study FluarixUS-005 will be a non-inferiority study of Fluarix in the pediatric population that would provide support for licensure in the pediatric population. Discussion are underway between CBER and GSK regarding [redacted]

15 Labeling

- Labeling negotiations were completed on July 15, 2005, which were several weeks prior to approval. The applicant desired to ship Fluarix to the United States in order to have sufficient supply in the United States for the fall influenza season. Therefore, CBER provided labeling comments through a series of teleconference, secure email, and regular email communications. A final printed label was agreed upon July 15, 2005 by the applicant and CBER. The following bullet points highlight the major changes to the applicant's original label:
    - The amounts of the stated excipients were included.
    - The epidemiology of influenza infection was significantly shortened with large sections eliminated from the label.
    - A post-hoc analysis of pooled immune response data from the Geriatric population were included.
    - The reference to concomitant administration with pneumococcal vaccine was eliminated.
    - The precautions section contained the same information but the order was rearranged.
    - The 95% confidence intervals for the solicited adverse events were included in the adverse events section.
    - The deaths observed in clinical trials of Fluarix were included.
    - Additional postmarketing adverse events were included.

- The lengthy discussion of Guillain-Barre syndrome was eliminated but the reference to the ACIP discussion of Guillain-Barre syndrome was maintained.