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).

Results 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 $\geq$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

Reported symptoms in the period from day of vaccination to 3rd day after vacc.		adults age group 18-60 yrs		elderly age group > 60 yrs	
		n= 59		n= 55	
		n	%	n	%
Local reactions					
Redness	intensity 1	9	15,3	5	9,1
	intensity 2	4	6,8	5	9,1
	intensity 3	2	3,4	2	3,6
	total:	15	25,4	12	21,8
Pain	intensity 1	17	28,8	7	12,7
	intensity 2	9	15,3	3	5,5
	intensity 3	0	0,0	0	0,0
	total:	26	44,1	10	18,2
Induration	intensity 1	12	20,3	13	23,6
	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**				
Fever	intensity 1	1	1,7	0	0,0
	intensity 2	0	0,0	0	0,0
	intensity 3	0	0,0	0	0,0
	total:	1	1,7	0	0,0
Shivering	intensity 1	2	3,4	5	9,1
	intensity 2	1	1,7	0	0,0
	intensity 3	0	0,0	0	0,0
	total:	3	5,1	5	9,1
Fatique	intensity 1	7	11,9	3	5,5
	intensity 2	2	3,4	3	5,5
	intensity 3	0	0,0	0	0,0
	total:	9	15,3	6	10,9
Headache	intensity 1	4	6,8	2	3,6
	intensity 2	4	6,8	0	0,0
	intensity 3	0	0,0	0	0,0
	total:	8	13,6	2	3,6
Sweating	intensity 1	2	3,4	2	3,6
	intensity 2	1	1,7	0	0,0
	intensity 3	0	0,0	0	0,0
	total:	3	5,1	2	3,6
Myalgia	intensity 1	8	13,6	3	5,5
	intensity 2	2	3,4	1	1,8
	intensity 3	0	0,0	0	0,0
	total:	10	16,9	4	7,3
Arthralgia	intensity 1	1	1,7	3	5,5
	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

		day 0			day 21		
		A/New-Caledonia (H1N1)	A/ A/Wyoming (H3N2)	B/ Jiangsu	A/New-Caledonia (H1N1)	A/ A/Wyoming (H3N2)	B/ Jiangsu
Age group	N	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.