Application Type	Efficacy Supplement
STN	125127/513
CBER Received Date	February 14, 2012
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Division / Office	DVRPA /OVRR
Priority Review	No
Reviewer Name(s)	Sahera Dirajlal-Fargo D.O Medical Officer, Clinical Review Branch 1
Review Completion Date / Stamped Date	12/12/2012
Supervisory Concurrence	Jeffrey Roberts, M.D. Chief, Clinical Review Branch 1
Applicant	GlaxoSmithKline Biologicals
Established Name	Influenza Virus Vaccine
(Proposed) Trade Name	Fluarix Quadrivalent
Pharmacologic Class	Vaccine
Formulation(s), ----(b)(4)-------, etc	Each dose contains 15 µg of the following antigens (60 µg total): A/ (H1N1), A/ (H3N2), B/ Victoria and B/ Yamagata
Dosage Form(s) and Route(s) of Administration	0.5 mL suspension for intramuscular injection, supplied in a single dose pre-filled syringe
Dosing Regimen	• In children 3 through 8 years of age. Previously unvaccinated with influenza vaccine receive two 0.5-mL doses; each 0.5-mL dose is administered at least 4 weeks apart. Previously vaccinated with any influenza vaccine in a prior season, receive one dose or two doses (0.5-mL each) depending on vaccination history as per the annual Advisory Committee on Immunization Practices (ACIP) Recommendation on Prevention and Control of Influenza with Vaccines. • Persons 9 years of age and older: One 0.5-mL dose.
Indication(s) and Intended Population(s)	Active immunization for the prevention of disease caused by influenza A subtype viruses and B lineage viruses contained in the vaccine.

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GLOSSARY

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
BLA	Biologics License Application
BLS	Biologics License Application supplement
CBER	Center for Biologics Evaluation and Research
CI	Confidence Interval
CFR	Code of Federal Regulations
CRF	Case Report Form
CSR	Clinical Study Report
D-QIV	Fluarix Quadrivalent
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
GMT	Geometric Mean Titer
HA	Hemagglutinin
HAI	Hemagglutination Inhibition Assay
LL	Lower Limit
MedDRA	Medical Dictionary for Regulatory Activities
PeRC	Pediatric Review Committee
PI	Package Insert
PMC	Postmarketing Commitment
PMR	Postmarketing Requirement
PREA	Pediatric Research Equity Act
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCR	Seroconversion Rate
SOC	System Organ Class
STN	Submission Tracking Number
TIV 1	Licensed Fluarix Trivalent Inactivated Influenza Vaccine
TIV 2	Fluarix formulation containing the alternative lineage B strain as contained in D-QIV instead of the WHO/CBER recommended strain
US	United States
VRBPAC	Vaccines and Biological Products Advisory Commitee
WHO	World Health Organization

1. EXECUTIVE SUMMARY

Fluarix Quadrivalent (D-QIV) is a quadrivalent, inactivated seasonal influenza vaccine. Fluarix Quadrivalent contains antigens from two influenza A subtype viruses (from subtypes H1N1 and H3N2) and two type B viruses (from two lineages, represented by the B/Victoria/2/87 and B/Yamagata/16/88 strains). The Fluarix Quadrivalent formulation utilizes the same starting materials (thimerosal-free inactivated split virus bulks and excipients) and manufacturing and control processes, equipment and facilities, as currently licensed for the Fluarix trivalent vaccine and will also be presented as a suspension for injection, in (b)(4) glass pre-filled (single-use) syringes. However,

compared to Fluarix (trivalent formulation), the major diffences with Fluarix Quadrivalent, are that Fluarix Quadrivalent contains a 4th antigen and a higher a total amount of hemagglutinin antigen (60 µg HA/dose) and higher total amount of inactive ingredients.

1.1 Recommendation for Regulatory Action

In the opinion of the clinical reviewer, the data submitted by the Applicant support the approval of Fluarix-Quadrivalent for active immunization of persons 3 years of age and older against influenza disease caused by the influenza subtypes A and lineage B viruses contained in the vaccine.

The recommendation is based on immunogenicity and safety data from four clinical trials. Effectiveness in children ages 3 through 17 years and adults ages ≥18 years were primarily supported by immunogenicity data from studies D-QIV-003 and D-QIV-008, respectively. In both studies, control groups received one of two formulations of trivalent influenza vaccine (Fluarix) [TIV-1, TIV-2], each containing an influenza lineage B virus that corresponded to one of the two lineage B viruses (B/Victoria or B/Yamagata) in Fluarix Quadrivalent. Antibody responses to Fluarix Quadrivalent were non-inferior to TIV antibody responses for influenza A subtypes and corresponding B lineages, and statistically higher to the opposite B lineage (e.g. B\Yamagata in D-QIV vs. B\Victoria in TIV-1). In individuals age ≥6 years, common adverse events reported after Fluarix Quadrivalent vaccination were injection site pain, muscle ache, headache and fatigue. Children age 3 to 5 years commonly developed drowsiness, irritability and loss of appetite. In children 3 through 8 years of age who received a second dose, the incidences of solicited adverse events were generally lower after the second dose than after the first dose.

1.2 Recommendation on Postmarketing Actions

The applicant is conducting a clinical endpoint efficacy study, D-QIV-004, in children age 6 through 35 months. The trial was initiated in October 2011 and data are expected to be available in 2013. This study is a postmarketing requirement under PREA.

The applicant has agreed to establish a pregnancy registry as a postmarketing commitment. The protocol will be submitted by april 30th, 2013 and the registry will be established by August 30th, 2013.

1.3 Summary of Clinical Findings

Studies D-QIV 008 and D-QIV 003 were the pivotal studies to support the safety and immunogenicity (inferred effectiveness) of Fluarix Quadrivalent.

Study D-QIV 008 was a Phase III safety, immunogenicity and lot consistency trial in 4656 healthy adults ages ≥18 years. Subjects were randomized in a 5:5:5:5:3 to receive one of three Fluarix Quadrivalent (D-QIV) vaccine lots, or Fluarix trivalent vaccine that contained a WHO/CBER-recommended influenza lineage B strain (B/Victoria) [TIV-1] or an alternative lineage B strain (B/Yamagata) [TIV-2]. The influenza B strains

contained in TIV-1 and TIV-2 are both included in D-QIV. A total of 3036 subjects received D-QIV (three lots combined), 1010 received TIV-1, and 610 received TIV-2. The co-primary objectives were to demonstrate lot-to-lot consistency for the three D-QIV vaccine lots, non-inferiority of antibody responses after D-QIV vaccination compared to antibody responses after TIV-1 or TIV-2 vaccination for influenza A subtypes and matched influenza B lineage, and superiority to the alternate influenza B lineage strain (e.g., B\Victoria in D-QIV vs. B\Yamagata in TIV-2). Lot to lot consistency criteria were met if the limits of the two-sided 95% CI for the largest GMR among the three lots were in between 0.67 and 1.5. Non inferiority criteria were met if the upper limit of the two-sided 95% CI for the GMT ratio (TIV-1/D-QIV) did not exceed 1.5 for each strain in the TIV vaccines and the upper limit of the two-sided 95% CI for the difference in SCR (TIV minus D-QIV) did not exceed 10% for each strain included in the TIV vaccines. The criteria for meeting superiority were met if the lower limit of the two-sided 95% CI for the GMT ratio was >1 and the lower limit of the two-sided 95% CI for the difference in SCR was > 0.

The lot to lot consistency criteria were met for all four influenza strains. Also, the criteria for non-inferiority and superiority of D-QIV to TIV-1 and TIV-2 were met for each respective strain in terms of GMT and SCR. The antibody response to the influenza B strain in D-QIV was superior to the trivalent vaccine's cross-reactive antibody response to the influenza B strain not contained in the trivalent vaccine.

A total of 3036 subjects who received D-QIV in Study D-QIV-008 were included in the safety population. Safety parameters evaluated included solicited, unsolicited, serious adverse events and deaths. For all study groups, injection site pain was the most frequent solicited local reaction, and occurred at similar rates (36% D-QIV, 37% TIV-1, 31% TIV-2). The most common solicited systemic AEs after D-QIV vaccination included fatigue (16%), headache (16%) and muscle ache (16%). None of the deaths or serious adverse events reported were considered related to the study vaccination.

Study Fluarix-D-QIV 003 was a Phase III, immunogenicity and safety study double-blinded, parallel group, multi-center trial. A total of 2750 children ages 3-17 years old were enrolled and randomized in a 1:1:1 ratio to receive Flu D-QIV, TIV-1 or TIV-2. A total of 915 subjects received D-QIV, 912 subjects received TIV-1 and 911 subjects received TIV-2. The co-primary objectives were to demonstrate non-inferiority of antibody responses after D-QIV vaccination compared to corresponding response after TIV-1 or TIV-2 vaccination, for the influenza A subtypes and matched B lineage. The secondary objectives was to evaluate superiority of D-QIV antibody responses compared to TIV-1 and TIV-2, for the B strain included in D-QIV but not in the trivalent vaccine. Criteria to meet non-inferiority and superiority were the same as the criteria described for study D-QIV 008.

The primary objectives to demonstrate non-inferiority of D-QIV to TIV (influenza A subtypes and B lineages) were met. For each strain, the upper 95% confidence limit for the GMT ratio (TIV/D-QIV) was <1.5 and the upper 95% confidence limit for SCR (TIV minus D-QIV) was <10% (Table 6).

The secondary objectives to demonstrate superiority of D-QIV to TIV (alternate B lineage) were met. The lower 95% confidence limit for the GMT ratio was >1, and the lower 95% confidence limit for the difference in SCR was >0, in terms of adjusted GMT ratios and SCR differences were met for both influenza B strains that were not included in the respective TIV (Table 7).

A total of 905 children who received D-QIV were included in according to protocol for safety cohort. Injection site pain was the most frequent local adverse event (49%) reported by children in the D-QIV group, followed by injection site redness (25%) and swelling (22%). In children younger than 6 years old, 23% of subjects experienced drowsiness, 22% irritability and 20% loss of appetite. For children six years of age and older, fatigue (21%), muscle aches (19%) headache (18%), arthralgia (11%) and gastrointestinal symptoms (11%) were the most common solicited AEs. The rates of solicited and unsolicited local and general AE's were similar among the 3 arms in children 3-17 years old. There was one accidental death during the study. Eight subjects in the D-QIV arm reported serious AEs and none were judged to be study related.

There were no individual safety concerns or pattern of safety concerns associated with the administration of Fluarix Quadrivalent.

1.4 Compliance with Pediatric Research Equity Act (PREA)

The pediatric development plan for Fluarix Quadrivalent was presented to and approved by the Pediatric Review Committee on October 24th, 2012. For children 3 years and older, the PREA requirement was fulfilled by safety and immunogenicity (inferred effectiveness) data from studies D-QIV-002 and D-QIV-003.

The applicant initiated, as part their clinical development plan, an evaluation of Fluarix Quadrivalent in children 6 months through 35 months of age (study D-QIV-004). The trial is ongoing and clinical endpoint efficacy data are expected to be available in 2013. The PREA requirement for this age group was deferred, since waiting for the data from D-QIV-004 would delay the availability of D-QIV for individuals ≥3 years of age.

A waiver was granted for children from birth to < 6 months of age because available data indicate that serum antibody responses to inactivated influenza vaccines in infants < 6 months of age are not as robust as in older children due to inherent immaturity of the immune system and interference from maternal antibody. Initiation of Fluarix Quadrivalent vaccination at <6 months of age would provide no meaningful therapeutic benefit over starting vaccination at 6 months of age, and the vaccine is not likely to be used in a substantial number of infants < 6 months of age.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Influenza infection in the United States is characterized by seasonal epidemics, usually occurring during the winter months. CDC estimates that from the 1976-1977 season to the 2006-2007 flu season, flu-associated deaths ranged from a low of about 3,000 to a high of about 49,000 people 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 persons who should be targeted for routine administration of influenza vaccine; in 2010 the ACIP recommended annual seasonal influenza vaccination for all persons over 6 months of age in the U.S.

The currently licensed inactivated seasonal influenza vaccines contain two influenza A virus subtypes and a single influenza B virus. There are two distinct lineages of influenza B virus: Victoria and Yamagata. The Vaccines and Related Biological Products Advisory Committee (VRBPAC) consisting of influenza experts convenes yearly and recommends which influenza strains should be included in the vaccine for the influenza season. Currently, an influenza B strain from one of the two influenza B lineages is included in the yearly trivalent vaccine. The influenza B strain recommended for use in the yearly trivalent vaccine has been matched to the main circulating influenza B strain only in one-half of the influenza seasons in the last eight years and the influenza B viruses from both lineages have circulated during the influenza season on several occasions. At a 2009 meeting of the VRBPAC panelists suggested expanding influenza vaccines to contain 4 virus strains: A/H1N1, A/H3N2, and 1 strain from each of the 2 type B lineages. On February 2012, VRBPAC voted to include vaccine strain B/Bisbane/60/2008 from the Victoria lineage if a quadrivalent influenza vaccine were available.

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

Influenza vaccines have been available since the 1940s. There are currently nine trivalent, inactivated, split-virion vaccines licensed in the U.S. for prevention of seasonal influenza in adults, including Fluarix. Fluarix was initially licensed in the U.S. on August 31, 2005 for the prevention of influenza subtypes A and B contained in the vaccine under the accelerated approval regulations; the indication was based on the immune response elicited by Fluarix in clinical studies. Like Fluarix, Afluria™, FluLaval™ and Fluzone™ HD were approved using the accelerated approval mechanism because of the shortage of influenza vaccine. Accelerated approval of these four vaccines was based on immunogenicity and safety data from studies using a surrogate marker (anti-hemagglutinin antibody response) for clinical efficacy. This is the first supplemental BLA to provide clinical data to support the approval of an inactivated quadrivalent influenza vaccine.

A live attenuated trivalent vaccine, FluMist Flumist Quadrivalent, is also licensed in the U.S. for the prevention of influenza illness in healthy subjects 2-49 years of age. A

quadrivalent formulation of Flumist was approved on March 9th 2012 and is the only quadrivalent influenza vaccine currently licensed in the U.S.

2.3 Safety and Efficacy of Pharmacologically Related Products

Fluarix Quadrivalent is manufactured using the same process as the Fluarix trivalent formulation.

Safety and immunogenicity data from two clinical studies in adults (N=3036) and children (N=915) were submitted to support the effectiveness and safety of Fluarix Quadrivalent. The trivalent formulation, Fluarix was first approved on August 31, 2005 based on the results of immunogenicity and safety studies. The efficacy of Fluarix was confirmed in a clinical endpoint study in Fluarix-US-006 in 2007.

The most common adverse events reported after influenza vaccines are solicited adverse reactions, particularly pain at the injection site, headache, fatigue, and myalgia.

Hypersensitivity reactions, including anaphylaxis, have been reported after influenza vaccination. These reactions have been uncommon (0-10 per million doses vaccine).

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

Fluarix Quadrivalent has not been licensed by any other regulatory authorities. However, Fluarix has been marketed globally since 1992. Please refer to the Fluarix package insert for more information regarding previous human experience with Fluarix in subjects 3 years of age and older.

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

Fluarix Quadrivalent studies for US licensure were conducted under IND 14473. Protocols for D-QIV 008 and 003 were submitted on August 24th 2010, and an outline of plans for sBLA submission was submitted on December 16th 2011.

This supplemental BLA was submitted on February 14th 2012. Subsequent clinical submissions to the BLA include:

- March 9th 2012- amendment 1, protocol deviation data by site number and by patient id number,
- June 26th 2012 - amendment 4 containing sensitivity analysis excluding all subjects from Romania site,
- August 16th 2012- amendment 8, sensitivity analysis of immunogenicity and safety by country, rate and prior influenza vaccination history for study D-QIV 008 and 003.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty or an unreasonable number of requests for additional information.

3.2 Compliance with Good Clinical Practices and Submission Integrity

The Applicant reported that all studies were conducted in accordance with Good Clinical Practice, the 1996 Declaration of Helsinki, the US Code of Federal Regulations and local rules and regulation of the countries.

The applicant notified CBER of issues with study conduct at one of the study sites for Study D-QIV 008. GSK received information from ----------(b)(6)---------- ---------- at site #81395 accusing the PI of misconduct, including filling out the diary cards herself. Subsequently GSK audited the site and found serious issues with the study contact. A total of 45 subjects (1% of total subjects) were enrolled at this site, a sensitivity analysis was conducted with these results omitted and did not affect the study results.

CBER Bioresearch Monitoring (BIMO) issued seven high-priority inspection assignments covering seven clinical investigators. The BIMO inspections did not reveal any problems that would impact the data submitted in the BLA.

3.3 Financial Disclosures

According to the Applicant, it is GSK policy to not compensate investigators in a way in which the compensation is affected by study outcome. Therefore, there are no disclosures for compensation that might have affected the outcome of the studies in this supplement [as required in 21 CFR 54.2 (a), (b), and (f)]. There were also no significant payments ($25,000 or more) to any clinical investigator, and no investigator had a $50,000 or more equity interest in the study vaccine [as required in 21 CFR 54.4 (a)(3)(iii-iv), 54.2(b-c)].

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

4.1 Chemistry, Manufacturing, and Controls

Please see review memoranda from Olga Zoueva and Priscilla Pastrana for details.

Data and information included in the supplement demonstrate that the manufacturing process is well controlled with appropriate validations, quality control testing, and stability data. Except for the addition of a second influenza type B virus in the formulation step and other quality control (QC) testing-related changes, the manufacture of Fluarix Quadrivalent is identical to Fluarix.

The container closure integrity test (CCIT) performed on (b)(4) used for storage of monovalent and final bulks was not considered acceptable by the CBER, ----------(b)(4)----------.

4.2 Clinical Assays

Please see review memos from Olga Zoueva for assay methods, and from Tielin Qin and Sirota Lev for the statistical analyses of the assay performance.

In the four studies of Fluarix Quadrivalent the hemagglutination-inhibition (HI) assay was used to measure the humoral immune response against each of the influenza strains contained in the Fluarix Quadrivalent candidate vaccines or the trivalent comparator vaccines (i.e., A/H1N1, A,/H3N2, B/Victoria and B/Yamagata).

HI antibody titers pre- and post-vaccination were used to measure vaccine activity in phase 3 studies FLU D-QIV-003 and FLU D-QIV-008. For FLU D-QIV-003, the HAI assay was performed in the -(b)(4)- laboratory and for FLU D-QIV-008 the HI assay was performed at the -(b)(4)- laboratory. The assay validations for these laboratories were provided and were found to be acceptable. The HI assays for the phase 1/2 studies were conducted in GSK's (b)(4) laboratory. The assay performance at the (b)(4) laboratory was not fully validated, but the immunogenicity results from the phase 1/2 studies were only supportive, will not be included in the label, and therefore, do not affect the recommendations for use of Fluarix Quadrivalent.

In study D-QIV-003 a ----------(b)(4)---------- assay was used to measure antibodies against the 4 strains contained in the D-QIV vaccine in a subset of subjects. The statistical reviewer found that the applicant has not demonstrated that the (b)(4) assay performance is linear and precise over the entire assay range. Immunogenicity evaluations using the (b)(4) assay were included as a secondary objective and were not the primary basis for inferring effectiveness of Fluarix Quadrivalent. The deficiencies therefore do not affect the overall recommendations for use of Fluarix Quadrivalent

4.3 Nonclinical Pharmacology/Toxicology

Results from a reproductive and developmental toxicology study were reviewed by CBER reviewer Dr. Steven Kunder. No safety signals were identified.

4.4 Clinical Pharmacology

No human pharmacology data were submitted in this application.

4.4.1 Mechanism of Action

Vaccination against influenza results in hemagglutination inhibition antibody titers. Specific levels of antibody have not been absolutely correlated with protection from

influenza illness. In some studies, HI antibody titers of ≥ 1:40 have been associated with protection from influenza illness in up to 50% of subjects.

4.4.2 Human Pharmacodynamics (PD)

N/A

4.4.3 Human Pharmacokinetics (PK)

N/A

4.5 Statistical

Please see Dr Ghebregiorgis's review memorandum for details.

Dr Ghebrgiorgis concluded that, in subjects 3 years of age and older, (a) D-QIV vaccine appears to provide non-inferior immunogenicity, compared to the licensed trivalent Fluarix vaccine, against four influenza strains. (b) Safety data indicated that the reactogenicity and safety profile of the D-QIV vaccine is similar to the profile of the trivalent Fluarix vaccine and a second Fluarix trivalent formulation (TIV-2) containing the B strain from the alternate lineage.. No safety concerns were identified. (c) Increasing the total antigen content by adding a fourth strain in the D-QIV vaccine does not appear to have a negative impact on the reactogenicity and safety profile relative to the trivalent Fluarix vaccine.

4.6 Pharmacovigilance

The applicant's pharmacovigilance plan was reviewed by Dr Patricia Rohan. No potential safety concerns were identified and routine pharmacovigilance was an acceptable strategy.

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

The clinical study reports, pertinent case report tabulations and forms (module 5) labeling (module 1.14), financial information (module 1.3.4), clinical overview (module 2.5), and integrated summary of efficacy and safety were reviewed.

5.1 Review Strategy

This review primarily focuses on the two pivotal studies D-QIV 008 (adults 18 years and older) and D-QIV 003 (children ages 3-18 years of age).

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

5.3 Table of Studies/Clinical Trials

Study	Type of clinical trial	Control*	Total # Subjects	Age (yrs)	Country
D-QIV 008	Randomized, double blind, immunogenicity	TIV-1, TIV-2	4046	≥ 18 years	US, Germany, Romania, Spain, Korea, Taiwan
D-QIV 003	Randomized, double blind, immunogenicity	TIV-1, TIV-2	3015	6months-17 years	US, Germany, Czech Republic, France, Philippines
D-QIV 001	Randomized, single-blind, immunogenicity	TIV-1	420	18-60 years	Czech Republic
D-QIV 002	Randomized, double-blinded, immunogenicity	TIV-1	599	18-47 months	Mexico

* TIV-1 refers to licensed Fluarix and TIV -2 refers to a trivalent Fluarix formulation containing the alternative lineage B strain (as contained in D-QIV) instead of the WHO/CBER strain.

5.4 Consultations

There were no consultations for this product application.

5.4.1 Advisory Committee Meeting (if applicable)

There were no regulatory issues or concerns that necessitated an advisory committee meeting discussion. Previous VRBPAC meetings have discussed the need for a Quadrivalent influenza vaccine, see section 2.1 for details.

5.4.2 External Consults/Collaborations

There were no external consults or collaborations for this application.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 D-QIV-008

A Phase III randomized, double- blinded, controlled study to evaluate the immunogenicity, reactogenicity and safety of quadrivalent influenza vaccine D-QIV and to evaluate clinical consistency of three production lots in terms of immunogenicity when administered to adults 18 years of age and older.

6.1.1 Objectives

The primary objectives of Study Flu D-QIV-008 were:
To assess the lot-to-lot consistency of three lots of D-QIV in terms of hemagglutination inhibition (HI) antibody geometric mean titers (GMTs)
To assess the immunological non-inferiority of the antibody response to influenza strains in D-QIV compared to the antibody response to the corresponding antigens in the trivalent vaccines (Two trivalent vaccines were used as active controls so that both influenza B strains could be compared to a single B strain included in the trivalent formulation. The trivalent formulations were: TIV-1, which was the marketed Fluarix vaccine for that influenza season and contained the two influenza A subtypes and the B strain recommended for that influenza seasons *and* TIV-2

vaccine, which was also a trivalent formulation but contained both influenza A subtypes and the altenative lineage B strain)
To assess the immunological superiority of the antibody response to the influenza B strain contained in D-QIV compared to the cross-reactive antibody response to the influenza B strain in TIV-1 and TIV-2 that was not included in each TIV vaccine

The secondary objectives were:
- To describe the immunogenicity of D-QIV, TIV-1 and TIV-2 21 Days post vaccination in each age stratum.

- To assess the reactogenicity and safety of D-QIV, TIV-1 and TIV-2 vaccines over all and in each age stratum in terms of solicited local and general symptoms for the 7 Days post vaccination, unsolicited symptoms during the 21 Day period post vaccination, and serious adverse events (SAEs) and medically attended adverse events and adverse events of special interest during the entire study period.

6.1.2 Design Overview

Study D-QIV 008 was a Phase III, randomized, double blinded, controlled study to evaluate the safety and immunogenicity of a quadrivalent influenza vaccine compared to TIV in adults. Healthy adult subjects ages 18 and older were randomized 5:5:5:5:3 to receive D-QIV from lot 1, D-QIV from lot 2, D-QIV from lot 3, TIV-1 or TIV-2. Subjects were seen in clinic on Day of vaccination. Subjects in the D-QIV and TIV-1 arms were followed for 6 months for safety and reactogenicity while subjects in the TIV-2 arms was given open-label vaccine and were followed until Day 21.

A subset of subjects (protocol planned 600 from each arm) were included in an immunogenicity subset. These subjects had blood specimens for immune response data collected at baseline and Day 21.

6.1.3 Population

The study enrolled healthy males and females who were 18 years of age and older at the time of vaccination. Exclusion criteria were as follows: a history of hypersensitivity to a previous dose of influenza vaccine or a history of allergy or reactions likely to be exacerbated by any vaccine component; received an influenza vaccine 6 months preceding the study or who had received any other vaccine within 30 Days before the study; had chronic pulmonary or cardiovascular disease, renal dysfunction, hepatic dysfunction, immunosuppresion, or history of Guillain-Barré Syndrome; had acute fever illness; had a child in care (a child who has been placed under the control or protection of an agency, or cared for by foster parents or living in a home care).

6.1.4 Study Treatments or Agents Mandated by the Protocol

Study subjects were randomized to receive one of three lots of D-QIV, TIV-1, or TIV-2.

TIV- 1 was the Fluarix formulation marketed during the 2010-2011 influenza season; therefore, the influenza antigens used in TIV-1were those recommended for the Northern Hemisphere 2010-2011 influenza season. Each dose of TIV-1 contained 15 µg of the following antigens (45 µg total):

A/California/7/2009 (H1N1),
A/Victoria/210/2009 (H3N2), and

B/Brisbane/60/2008.

TIV-2 contained the two influenza strains recommended for the 2010-2011 influenza season. The influenza B strain in TIV-2 was the influenza B strain from the different lineage than the influenza B strain recommended for use during the 2010-2011 season and therefore different from the B strain contained in TIV-1 or Fluarix. Each dose of TIV-2 contained 15 µg of the following antigens (45 µg total):

A/California/7/2009 (H1N1),
A/Victoria/210/2009 (H3N2), and
B/Brisbane/3/2007

D-QIV was a quadrivalent inactivated influenza vaccine, three of the four strains were the same as those recommended for the 2010-2011 influenza season and included in TIV-1 (Fluarix), the fourth strain was the influenza B strain from a different lineage that was included in TIV-2. Each dose contained 15 µg of the following antigens (60 µg total):
A/California/7/2009 (H1N1),
A/Victoria/210/2009 (H3N2),
B/Brisbane/60/2008. and
B/Brisbane/3/2007

D-QIV and both formulations of TIV are thiomerosal free and presented as pre-filled syringes with an injectable volume of 0.5 mL.

6.1.6 Sites and Centers

This study was conducted in 43 centers in Germany, Romania, Spain, Korea, Taiwan and the United States.

6.1.7 Surveillance/Monitoring

Subjects were seen at the study site on Day 0 and Day 21. The Day 21 visit was the final study visit for subjects in the TIV-2 arm; subjects in the FLU D D-QIV and Fluarix arms were contacted by telephone for safety follow-up on Day 180.

Medical history was obtained prior to vaccination on Day 0; a physical examination was also performed prior to vaccination. A symptom-directed physical examination was performed at the Day 21 visit if deemed necessary by the investigator. Vital signs including body temperature, blood pressure, heart rate, respiratory rate were assessed prior to vaccination. A urine pregnancy test was obtained for all females of childbearing potential prior to vaccination.

Subjects were observed for 30 minutes after vaccination. Diary cards were distributed; subjects were instructed on how to complete the diary card and asked to return the diary card at the Day 21 visit.

Information on solicited adverse reactions was collected for seven Days after vaccination (Day of vaccination and subsequent six Days). The solicited local adverse reactions followed were pain, redness, and swelling at the injection site. Pain was graded in intensity as none (Grade 0), mild (present but not interfering with daily activities, Grade 1), moderate (painful when limb is moved and interferes with daily activity, Grade 2), or severe (significant pain at rest that prevents normal activities, Grade 3). The greatest surface diameter of redness and swelling was recorded in millimeters. The maximum intensity of redness and/or swelling was scored as Grade 0 (≤ 20 mm), Grade 1 (≥ 20 - ≤ 50 mm), Grade 2 (≥ 50 - ≤ 100 mm), and Grade 3 (> 100 mm).

The solicited general adverse reactions followed were fever, headache, fatigue, gastrointestinal symptoms (nausea, vomiting, diarrhea, and/or abdominal pain), joint pain, muscle aches (generalized / widespread), and shivering. All solicited systemic adverse reactions were graded in intensity as none (Grade 0), mild (present but no effect on normal daily activity, Grade 1), moderate (interferes with normal activity, Grade 2) and severe (prevents normal activity, Grade 3). Fever was recorded as degrees on the Diary Card, and temperature of ≥ 39.0° C/ 102.2° F was scored as Grade 3.

Information on medically attended AEs, potential immune mediated diseases, and serious AEs were collected for the entire 180 Day study period for subjects in the FLU D D-QIV and TIV-1 (Fluarix) arms.

Information on all concomitant medications received by subjects, except vitamins and dietary supplements, taken in the first 21 Days of the study were recorded in the Case Report Form. Information on concomitant medications administered to treat medically attended AEs, potential immune mediated diseases, and serious AEs were collected during the entire study period.

6.1.8 Endpoints and Criteria for Study Success

The primary endpoint was the serum HI antibody response against the four influenza vaccine strains at Day 0 and Day 21. The response was measured using geometric mean titers at baseline on Day 21 and by seroconversion rates at Day 21. Serconversion was defined as a pre-vaccination HI titer of < 1:10 with a post-vaccination titer ≥ 1:40 or at least a four fold increase in serum HI antibody titer over baseline to ≥ 1:10 following vaccination.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Treatment allocation at each study site was performed using an internet randomization system (SBIR). The randomization algorithm used a minimization procedure accounting for the center, previous influenza vaccination history for the 2009-2010 season and age (18-64 years or ≥ 65 years).

Flu D D-QIV and TIV-1 (Fluarix) were administered in a double-blinded design; TIV-2 was administered in an open label design. The laboratory in charge of HI assays was blinded to the treatment.

Primary immunogenicity analyses: Lot to lot consistency would be demonstrated if, for each vaccine strain, the limits of the two-sided 95% confidence interval for the largest geometric mean ration among the three lots were between 0.67-1.5. Non-inferiority would be demonstrated if 1) the upper limit of the two-sided 95% CI for the ratio of GMT of TIV-1 (Fluarix) vaccine or TIV-2 vaccine over D-QIV vaccine did not exceed 1.5 for each strain that was included in the TIV-1 (Fluarix) and TIV-2 vaccines and 2) if the upper limit of the two-sided 95% CI for the difference in SCR (TIV-1 [Fluarix] vaccine or TIV-2 vaccine minus D-QIV vaccine) did not exceed 10% for each strain that was included in the TIV-1 (Fluarix) and TIV-2 vaccines respectively. Immunologic superiority of the unique B strain in D-QIV vaccine (e.g., the influenza B strain included in the D-QIV but not in the TIV formulation being compared to D-QIV) was demonstrated if the lower limit of the two-sided 95% CI on GMT ratio (D-QIV vaccine over TIV-1 [Fluarix] vaccine or D-QIV vaccine over TIV-2 vaccine) was greater than 1 and the lower limit of the two-sided 95% CI for the difference in SCR (D-QIV vaccine minus TIV-1 [Fluarix] vaccine or TIV-2 vaccine) was greater than 0.

Secondary immunogenicity analyses included assessments of the proportion of subjects with four-fold increase in antibody titer, proportion with HA antibody titer greater than 1:40, and geometric mean titers.

The global power to meet all co-primary objectives was at least 90%.

There were three main study populations:
The Total Vaccinated Cohort included all vaccinated subjects.
The Total Vaccinated Cohort subset for analysis of safety included all subjects with vaccination documented.
The Total Vaccinated Cohort subset for analysis of immunogenicity included vaccinated subjects with immunogenicity endpoint measures available for analysis.

The primary cohort for the analysis of safety was the Total Vaccinated Cohort for safety. If the percentage of subjects excluded from the ATP cohort for analysis of safety was greater than 5%, a secondary safety analysis would be performed on the ATP cohort for analysis of safety subset. This cohort included all subjects who were vaccinated according to randomized assignment, for whom the site of vaccination was known, who had not received a vaccine forbidden in the protocol, and for whom there are sufficient data to perform an analysis of safety.

The primary analysis for immunogenicity was performed on the ATP cohort for analysis of immunogenicity. This cohort included subjects who met all eligibility criteria, complied with the study protocol, met no elimination criteria, and for whom immunogenicity measurements were available. The elimination criteria were use of investigational or non-registrational products other than study vaccine, administration of another vaccine in the period from seven Days before study vaccination to 21 Days after study vaccination, chronic administration of immunosuppressants or other immune-modifying drugs during the 21 Days post-vaccination, and administration of immunoglobulin or any blood product in the 21 Days post-vaccination.

6.1.10 Study Population and Disposition

Study D-QIV-008 was conducted by 43 principal investigators in six countries (Germany, Romania, Spain, Korea, Taiwan and the United States. The first subject was enrolled on 4 October 2010 and the last study contact was 6 June 2011.

6.1.10.1 Populations Enrolled/Analyzed

A total of 4656 subjects were randomized and vaccinated: 3036 (65%) were vaccinated with D-QIV, 1010 (22%) with TIV-1 and 610 (13%) with TIV-2. Of the subjects in the D-QIV group, 1012 were vaccinated with the D-QIV-1 lot, 1013 with D-QIV-2 lot, and 1011 with D-QIV 3 lot. Please see section 6.1.10.1.3 for details regarding subject disposition.

6.1.10.1.1 Demographics

The mean age for subjects in the D-QIV-1 arm was 57.7 years, in the D-QIV-2 arm was 58 years and in the D-QIV-3 arm was 57.9 years. The mean age in both the TIV-1 and TIV-2 arm was 58.1. The median age was either 64 or 65 years old in all arms. The minimum age was 18 and maximum age was 92 for both males and females. The majority of subjects in all arms were females (59.1% in D-QIV-1, 57.1% in D-QIV-2, 56.3% in D-QIV-3, 54.3% in TIV-1 and 56.2% in TIV-2). Most subjects were White (68.8% in D-QIV-1, 67.7% in D-QIV-2, 68.8% in D-QIV-3 69.2% in TIV-1 and 67.9% in TIV-2). In addition, 26% of subjects in all arms were East Asians, 3% were Africa American and fewer than 1% were of other races or ethnicities. The ethnicity and geographic ancestry distribution was similar within each age strata.

Reviewer comment: The baseline demographic characteristics were similar between all D-QIV lots and also between all study arms.

The demographic profiles for all arms in the ATP cohort for immunogenicity were comparable to those of the Total Vaccinated Cohort.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

History of influenza vaccination:
A total of 78.7% of subjects in the Total Vaccinated Cohort had received an influenza vaccination during the previous three influenza seasons: 78.9% in the D-QIV arm, 78% in TIV-1 arm and 79.2% in TIV-2 arm. 28% of subjects in the Total Vaccinated Cohort had received the H1N1 vaccination during the previous season.

Reviewer comment: The percentage of subjects who had been vaccinated in the previous year was similar between all study arms.

6.1.10.1.3 Subject Disposition

Of the 4656 subjects vaccinated, 4597 (98.7%) completed the study (2994 in the D-QIV arm, 1010 in the TIV1 arm and 610 in the TIV-2 arm). These 4597 subjects who completed the study composed the Total Vaccinated Cohort. The number of subjects vaccinated, completing the study, or withdrawing from the study is shown in the table below.

Table 1: D-QIV-008 - Subject Disposition

	D-QIV-1	**D-QIV-2**	**D-QIV-3**	**TIV-1**	**TIV-2**	**Total**
Total Vaccinated Cohort	1012	1013	1011	1010	610	4656
Administration of vaccine forbidden by protocol	1	5	2	1	2	11
Randomization failure	2	0	2	1	1	6
Vaccine not administered according to protocol	0	1	0	0	0	1
ATP cohort for safety	1009	1008	1006	1008	607	4638
Protocol violation	3	1	3	5	2	14
Non compliance with blood sampling schedule	7	11	7	7	6	38
Serological data missing	6	6	8	5	5	30
ATP cohort for analysis of immunogenicity	993	990	988	991	594	4556

Source: BLA 125127/ SN 513, CSR D-QIV 008, Table 22, page 79

In all, 1.4% of subjects in D-QIV arm, 1.3% of subjects in TIV-1 arm and 0.65% of subjects in TIV-2 arm prematurely discontinued the study. The most common reason for premature study discontinuation was lost to follow-up; the percentage of subjects who were lost to follow-up was similar D-QIV and TIV-1 and was less than 1% in both arms. Serious adverse events will be discussed later in the review.

Reviewer comment: The percentage of subjects who prematurely discontinued the study was small and similar between D-QIV and the TIV-1 arm. The percentage who prematurely discontinued the study was lower in the TIV-2 arm. This difference is due to the shorter follow-

up time for subjects in the TIV-2 arm (21 Days) compared to the D-QIV and TIV-1 arms (180 Days) Overall, these results suggests that the study was well conducted with adequate follow-up.

Additional subjects were excluded from the Total Vaccinated Cohort resulting in the ATP cohorts. The reasons for exclusion from the different cohorts are shown in the table below.

Table 2: D-QIV-008 - Number of Subjects Included in ATP Cohorts with Reasons for Exclusion from Study Population

	D-QIV-1	D-QIV-2	D-QIV-3	TIV-1	TIV-2	Total
Total Vaccinated Cohort	1012	1013	1011	1010	610	4656
Administration of vaccine forbidden by protocol	1	5	2	1	2	11
Randomization failure	2	0	2	1	1	6
Vaccine not administered according to protocol	0	1	0	0	0	1
ATP cohort for safety	1009	1008	1006	1008	607	4638
Protocol violation	3	1	3	5	2	14
Non compliance with blood sampling schedule	7	11	7	7	6	38
Serological data missing	6	6	8	5	5	30
ATP cohort for analysis of immunogenicity	993	990	988	991	594	4556

Source: BLA 125127/ SN 513, CSR D-QIV 008, Table 23, page 79

The majority of subjects were included in the ATP safety cohort (99.6%) and the ATP immunogenicity cohort (98.2%). The number of subjects who were excluded and the reasons for exclusion were similar between the study arms.

According to the applicant, subject compliance with the diary card was greater than 99% in the three study arms.

Reviewer comment: Since the applicant did not include the criteria used for compliance with the diary card, it is difficult to determine the usefulness of the finding that 99% of subjects were compliant.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

One of the co-primary objectives was to assess lot-to-lot consistency of three lots of D-QIV in terms of HI antibody GMTs. Lot consistency would be demonstrated if the limits of the two-sided 95% CI for the largest geometric mean ratio among the three lots were between 0.67-1.5 for each strain. The results are shown in the table below:

Table 3: D-QIV-008 – Adjusted GMT ratios of HI antibody at Day 21 for the Maximum Difference Among Two Lots of D-QIV (ATP cohort for immunogenicity)

	Adjusted GMT		**GMT ratio**		
	D-QIV1	**D-QIV 2**	**Value**	**LL 95% CI***	**UL 95% CI***
A/California/7/2009 (H1N1)	196.5	209	0.94	0.8	1.10
A/Victoria/210/2009 (H3N2)	306.8	330.6	0.93	0.81	1.06
B/Brisbane/60/2008	410.7	396.7	1.04	0.93	1.15
B/Brisbane/3/2007	605	599	1.01	0.90	1.13

*CI = confidence interval
Source: BLA 125127/ SN 513, CSR D-QIV 008, Table 28-31, page 86-87

As shown in the table above, D-QIV met the lot to lot consistency criteria for all four influenza strains. The immunogenicity from all 3 lots were pooled in subsequent analysis, eg: Table 4 and subsequent tables.
The other co-primary objective was to assess non-inferiority of the antibody response to influenza antigens in D-QIV compared to TIV in terms of HI antibody GMTs and seroconversion rates for the three strains that were included in each of TIV-1 and TIV-2. Seroconversion was defined as either a pre-vaccination HI titer <1:10 with a post-vaccination titer ≥ 1:40 or a pre-vaccination titer ≥1:10 with a four fold or greater increase in post-vaccination titer. Criteria for successfully demonstrating non-inferiority were if:
- the upper limit of the two-sided 95% CI for the ratio of Day 21 GMTs for TIV-1 or TIV-2 over D-QIV vaccine did not exceed 1.5 for each strain, and
- the upper limit of the two-sided 95% CI for the difference in seroconversion rate of TIV 1 or TIV2 minus D-QIV did not exceed 10% for each strain.
The results are shown in the table below.

Table 4: D-QIV-008 – Non-Inferiority of D-QIV versus TIV (TIV1 and TIV-2) in Terms of GMTs at Day 21 (ATP Cohort for Immunogenicity)

	Adjusted GMT		**GMT ratio**		
			Value	**LL 95% CI***	**UL 95% CI***
	TIV-1 or TIV-2	D-QIV	TIV/ D-QIV		
A/California/7/2009 (H1N1)	214.8	201.6	1.07	0.96	1.18
A/Victoria/210/2009 (H3N2)	312.2	318.5	0.98	0.90	1.07
	TIV-1	D-QIV	TIV-1/ D-QIV		
B/Brisbane/60/2008	395.3	404.2	0.98	0.90	1.07
	TIV-2	D-QIV	TIV-2/ D-QIV		
B/Brisbane/3/2007	584.7	600.8	0.97	0.89	1.07

*CI = confidence interval
Source: BLA 125127/ SN 513, CSR D-QIV 008, Table 32-34, page 88-89

Table 5: D-QIV-008 – Non-Inferiority of D-QIV versus TIV (TIV1 and TIV-2) in Terms of Seroconversion Rate Difference at Day 21 (ATP cohort for immunogenicity)

	Percentage of subjects with seroconversion		**Difference in seroconversion rate**		
			%	**LL 95% CI***	**UL 95% CI***

	Percentage of subjects with seroconversion		**Difference in seroconversion rate**		
			%	**LL 95% CI***	**UL 95% CI***
	TIV-1 or TIV-2	D-QIV	TIV minus D-QIV		
A/California/7/2009 (H1N1)	78.6	77.5	1.08	-2.03	4.11
A/Victoria/210/2009 (H3N2)	67.8	71.5	-3.71	-7.15	-0.30
	TIV-1	D-QIV	TIV-1 minus D-QIV		
B/Brisbane/60/2008	55.4	58.1	-2.71	-7.29	1.83
	TIV-2	D-QIV	TIV-2 minus D-QIV		
B/Brisbane/3/2007	59.1	61.7	-2.69	-7.47	2.01

*CI = confidence interval
Source: BLA 125127/ SN 513, CSR D-QIV 008, Table 35-37, page 90-91

Criteria for non-inferiority of D-QIV versus TIV were met for both analyses, comparison of GMT ratio on Day 21 and seroconversion rates, for all 4 strains.

Reviewer comment: There were no clear differences between the vaccine arms. The seroconversion rate were higher for D-QIV than TIV for all strains except A/California/7/2009 (H1N1) All results met the criteria for demonstration of non-inferiority as outlined in the FDA Guidance for Industry, "Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines," Although, these criteria were developed for the licensure of seasonal trivalent influenza vaccines using the accelerated approval mechanism, the fulfillment of these criteria in this study supports the non-inferiority comparison of D-QIV to TIV.

The final co-primary objective was to assess superiority of the antibody response to the influenza B strain in D-QIV versus to the cross-reactive antibody response to the influenza B strain of the opposite lineage. For example, the antibody response to the B strain of the Yamagata lineage should be greater for the D-QIV strain than for the antibody response to B/Yamagata in the TIV arm that included only the B/Victoria strain. Criteria for successfully meeting this objective were 1) the lower limit of the two-sided 95% CI on GMT ratio of D-QIV over TIV-1 or D-QIV over TIV-2 was greater than 1 and 2)the lower limit of the two-sided 95% CI for the difference in seroconversion rate was greater than 0. The results are shown in the table below.

Table 6: D-QIV-008 – Superiority of D-QIV versus TIV (TIV1 and TIV-2) in Terms of GMTs at Day 21 (ATP Cohort for Immunogenicity)

	Adjusted GMT		**GMT ratio**		
			Value	**LL 95% CI***	**UL 95% CI***
	D-QIV	TIV-2	D-QIV/ TIV-2		
B/Brisbane/60/2008	403.5	259.4	1.56	1.42	1.70
	D-QIV	TIV-1	D-QIV/TIV-1		
B/Brisbane/3/2007	601.2	387.7	1.55	1.41	1.70

*CI = confidence interval
Source: BLA 125127/ SN 513, CSR D-QIV 008, Table 38-39, page 92

Table 7: D-QIV-008 – Superiority of D-QIV versus TIV (TIV1 and TIV-2) in Terms of Seroconversion Rate Difference at Day 21 (ATP cohort for immunogenicity)

	Percentage of subjects with seroconversion		**Difference in seroconversion rate**		
			%	LL 95% CI*	UL 95% CI*
	TIV-2	D-QIV	D-QIV minus TIV-2		
B/Brisbane/60/2008	47.5	58.1	10.53	5.7	15.33
	TIV-1	D-QIV	D-QIV minus TIV-1		
B/Brisbane/3/2007	45.6	61.7	16.12	11.54	20.65

*CI = confidence interval
Source: BLA 125127/ SN 513, CSR D-QIV 008, Table 40-41, page 92-93

As shown in the table above, criteria for superiority of D-QIV versus TIV in terms of adjusted GMT ratio and seroconversion rate difference were met for both B strain that were not included in the respective TIV.

Reviewer comment: The antibody response to the influenza strain in D-QIV was superior to the cross-reactive antibody response to the influenza B strain of the opposite lineage. Therefore, vaccination with trivalent influenza vaccines does not result in an adequate antibody response to influenza B strains from both lineages, while vaccination with the quadrivalent formulation resulted in an adequate antibody response to both influenza B strains.

6.1.11.2 Analyses of Secondary Endpoints

Secondary endpoints included analysis of antibody response using seroconversion rates, the percentage of subjects with a HI titer ≥ 1:40 post-vaccination, and mean geometric increase (defined as the geometric mean ratios of the post-vaccination HI titer to the Day 0 HI titer). The results for these analyses are shown in the table below.

Table 8 : D-QIV 008- Seroconversion , % Subjects with HI titers ≥ 1:40 and Geometric Mean Increase for HI Antibodies at Day 21 (ATP Cohort for Immunogenicity)

		Seroconversion			**% subjects with HI titers ≥ 1:40**			**Mean Geometric Increase**		
Strain	**Group**	**%**	**LL 95% CI***	**UL 95% CI***	**%**	**LL 95% CI***	**UL 95% CI***	**Value**	**LL 95% CI***	**UL 95% CI***
A/California/7/2009 (H1N1)	D-QIV	77.5	75.5	79.4	91.3	89.9	92.5	13.69	12.7	14.76
	TIV-1	77.2	73.6	80.5	91.8	89.3	93.8	13.92	12.23	15.84
	TIV-2	80.2	76.5	83.5	92.7	90.2	94.8	14.88	12.91	17.16
A/Victoria/210/2009 (H3N2)	D-QIV	71.5	69.3	73.5	96.8	95.9	97.6	9.28	8.64	9.96
	TIV-1	65.8	61.9	69.6	95.9	94	97.3	7.84	6.93	8.88
	TIV-2	70	65.9	73.9	96.8	95	98.1	9.52	8.33	10.89
B/Brisbane/60/2008	D-QIV	58.1	55.8	60.4	98.8	98.2	99.3	5.48	5.12	5.85
	TIV-1	55.4	51.3	59.4	98.5	97.2	99.3	5.37	4.75	6.06
	TIV-2	47.5	43.2	51.9	96.1	94.1	97.5	3.60	3.25	3.98
B/Brisbane/3/2007	D-QIV	61.7	59.5	64	99.1	98.5	99.5	5.93	5.53	6.36
	TIV-1	45.6	41.6	49.7	97.9	96.4	98.9	3.84	3.42	4.30
	TIV-2	59.1	54.7	63.3	99.6	98.7	100	5.84	5.13	6.65

*CI = confidence interval
Source: BLA 125127/ SN 513, CSR D-QIV 008, Table 43, 44, 45, page 95-97

Reviewer's comment: All four arms met the criteria for demonstration of immunogenicity for seroconversion rate and for percentage of subjects with post-vaccination HI titer ≥ 1:40 as described for licensure of seasonal trivalent vaccines using the accelerated approval in the FDA Guidance for Industry, "Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines". Specifically, the lower bound of the 95% confidence interval for seroconversion was greater than 40% for all four strains and the percentage of subjects with HI titers of 1:40 or higher post-vaccination was greater than 70% for all four strains. It is interesting to note that even though the antibody responses to the influenza B strain in D-QIV were superior to the cross-reactive antibody responses to the opposite B lineage strain in the TIVs, these criteria for demonstration of immunogenicity as outlined in the Guidance were met for the cross-reactive antibody response to the influenza B strains that were not included in the individual B vaccines.

The immunogenicity results were also analyzed by age stratum and gender. The results by age stratum are shown in the following table. Because FDA defines elderly as 65 years of age and older, the results in this table are for the age groups, 18 to 64 years and 65 years and older.

Table 9 : D-QIV 008- Seroconversion ,Percentage of Subjects With a Serum HI Titers ≥ 1:40 and Geometric Mean Increase for HI Antibodies for 18-64 year Olds and Older Than 65 Year Olds at Day 21 (ATP cohort for immunogenicity)

		Seroconversion				**% subject with HI ≥ 1:40**			**Mean Geometric Increase**		
Strain	**Group**	**Age strata**	**%**	**LL 95% CI***	**UL 95% CI***	**%**	**LL 95% CI***	**UL 95% CI***	**Value**	**LL 95% CI***	**UL 95% CI***
A/California/7 /2009 (H1N1)	D-QIV	18-64y	82.7	80.1	85.1	94.8	93.2	96.1	19.53	17.58	21.7
		+65 y	71.9	68.8	74.9	87.5	95.1	89.6	9.32	8.42	10.32
	TIV-1	18-64y	79.3	74.4	83.6	94.6	91.5	96.8	17.5	14.46	21.17
		+65 y	74.9	69.5	79.8	88.7	84.5	92.1	10.88	9.18	12.9
	TIV-2	18-64y	81.5	76.4	86	94.9	91.6	97.2	18.66	15.18	22.93
		+65 y	78.8	73.3	83.6	90.3	86.1	93.7	11.75	9.68	14.25
A/Victoria/210 /2009 (H3N2)	D-QIV	18-64y	76.6	73.8	79.3	97.5	96.3	98.4	12.41	11.21	13.74
		+65 y	65.9	62.6	69.1	96	94.5	97.2	6.78	6.16	7.45
	TIV-1	18-64y	70.4	65	75.4	96.2	93.4	98	10.05	8.4	12.04
		+65 y	60.8	55	66.5	95.6	92.5	97.6	6	8.08	7.08
	TIV-2	18-64y	73.4	67.8	78.6	96	93	98	10.95	9.09	13.18
		+65 y	66.4	60.3	72.1	97.7	95	99.1	8.23	6.78	10
B/Brisbane/60/ 2008	D-QIV	18-64y	67.4	64.3	70.4	98.7	97.8	99.3	7.8	7.07	8.6
		+65 y	48	44.6	51.4	99	98	99.5	3.74	3.44	4.06
	TIV-1	18-64y	64.6	59.1	69.9	99.4	97.7	99.9	7.82	6.53	9.36
		+65 y	45.4	39.5	51.3	97.6	95.1	99	3.58	3.09	4.14
	TIV-2	18-64y	51.3	45.2	57.4	97.1	94.3	98.7	4.03	3.47	4.68
		+65 y	43.6	37.5	49.9	95	91.6	97.3	3.19	2.78	3.66
B/Brisbane/3/2 007	D-QIV	18-64y	66.9	63.8	69.9	99.3	98.5	99.7	7.63	6.87	8.48
		+65 y	56.2	52.8	59.5	98.9	97.9	99.4	4.51	4.14	4.92
	TIV-1	18-64y	48.7	43.1	54.4	97.1	94.6	98.7	4.72	4.72	5.66
		+65 y	42.3	36.5	48.2	98.6	96.5	99.6	3.07	3.07	3.5
	TIV-2	18-64y	60.5	54.4	66.4	99.3	97.4	99.9	6.70	6.7	8.19
		+65 y	57.5	51.3	63.6	100	98.6	100	5.06	5.06	5.95

*CI = confidence interval

Source: BLA 125127/ SN 513, CSR D-QIV 008Supplement 35-37, page 226-229

Reviewer's comment: Overall, seroconversion rates were lower in the subjects that were 65 years of age and older compared to subjects 18-60 years of age. This is likely because a greater percentage of subjects in the older age cohort had HI tiers ≥ 1:40 at baseline. (These data are not shown in this review). However all subjects in all four arms in both age strata met the criteria for demonstration of immunogenicity as outlined in the FDA Guidance for Industry, "Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines" for adults < 65 years of age for antigens included in the individual vaccines.

Immunogenicity results were also provided for subjects 75 years of age and older. These results are shown in the following table.

Table 10 : D-QIV 008- Seroconversion ,Percent of Subjects with HI Titers ≥ 1:40 and Geometric Mean Increase for HI Antibodies for 18-74 Year Olds and Older than 75 year Olds at Day 21 (ATP cohort for immunogenicity)

		Seroconversion				% subjects with HI Titers ≥ 1:40			Mean Geometric Increase		
Strain	**Group**	**Age strata**	**%**	**LL 95% CI***	**UL 95% CI***	**%**	**LL 95% CI***	**UL 95% CI***	**Value**	**LL 95% CI***	**UL 95% CI***
A/California/ 7/2009 (H1N1)	D-QIV	18-74y	78	75.8	80	92.1	90.7	93.4	14.54	13.39	15.78
		+75 y	74.7	68.8	80	86.1	81.1	90.1	9.42	7.86	11.29
	TIV-1	18-74y	78.8	75	82.3	92.1	89.4	94.2	14.91	12.94	17.18
		+75 y	68.1	57.5	77.5	90.1	82.1	95.4	9.46	6.94	12.89
	TIV-2	18-74y	80.5	76.6	84.1	92.8	90.1	95	15.26	13.06	17.81
		+75 y	78.1	66.9	86.9	91.8	83	96.9	12.74	8.85	18.34
A/Victoria/2 10/2009 (H3N2)	D-QIV	18-74y	72.3	70	74.5	97.1	96.2	97.9	9.84	9.11	10.62
		+75 y	66.3	60	72.1	94.8	91.3	97.2	6.45	5.37	7.74
	TIV-1	18-74y	66.9	62.7	71	96.3	94.3	97.8	8.25	7.2	9.44
		+75 y	59.3	48.5	69.5	93.4	86.2	97.5	5.90	4.32	8.06
	TIV-2	18-74y	70.9	66.5	75	96.5	94.4	98	9.85	8.52	11.39
		+75 y	64.4	52.3	75.3	98.6	92.6	100	7.70	5.35	11.09
B/Brisbane/6 0/2008	D-QIV	18-74y	61.5	59.1	64	98.8	98.1	99.3	6.07	5.65	6.53
		+75 y	36.5	30.6	42.9	99.2	97.2	99.9	2.88	2.51	3.32
	TIV-1	18-74y	57.6	53.2	61.9	98.5	97	99.3	5.93	5.19	6.78
		+75 y	42.9	32.5	53.7	98.9	94	100	3.04	2.37	3.9
	TIV-2	18-74y	48.8	44.1	53.5	96.3	94.2	97.8	3.71	3.32	4.15
		+75 y	39.7	28.5	51.9	94.5	86.6	98.5	2.95	2.33	3.75
B/Brisbane/3 /2007	D-QIV	18-74y	64	61.5	66.4	99.1	98.5	99.5	6.38	5.91	6.89
		+75 y	47.8	41.4	54.2	98.8	96.5	99.8	3.76	3.21	4.40
	TIV-1	18-74y	46.3	41.9	50.7	97.7	96	98.8	4	3.52	4.55
		+75 y	41.8	31.5	52.6	98.9	94	100	3.05	2.43	3.84
	TIV-2	18-74y	60.4	55.7	64.9	99.6	98.4	99.9	6.13	5.31	7.07
		+75 y	50.7	38.7	62.6	100	95.1	100	4.34	3.24	5.79

*CI = confidence interval

Source: BLA 125127/ SN 513, CSR D-QIV 008, Supplement 39-41, page 231-234

Reviewer's comment: Of interest, the criteria for demonstration of immunogenicity described in the FDA Guidance were also met for subjects 75 years of age and older.

6.1.11.3 Subpopulation Analyses

Subgroup analyses were provided by country, previous vaccination, sex, and ethnicity.

By country:
The results for the primary end-points for subjects enrolled in the United States were compared to results from subjects enrolled in all other countries (Germany, Romania, Spain, Korea, Taiwan). The results are shown in the table below.

Table 11 : D-QIV 008- Data for Non-Inferiority and Superiority of D-QIV versus the Trivalent Vaccines in Terms of GMT and SCR by Country

Country	Strain	Non-Inferiority by GMT	Non-Inferiority by SCR	Superiority by GMT	Superiority by SCR
United States	A/California/7/2009 (H1N1)	Met criteria	Met criteria	Met criteria	Met criteria
	A/Victoria/210/2009 (H3N2)	Met criteria	Met criteria	Met criteria	Met criteria
	B/Brisbane/60/2008	Met criteria	Met criteria	Met criteria	Did not meet criteria
	B/Brisbane/3/2007	Met criteria	Did not meet criteria	Met criteria	Met criteria
Germany	A/California/7/2009 (H1N1)	Met criteria	Did not meet criteria	Met criteria	Met criteria
	A/Victoria/210/2009 (H3N2)	Met criteria	Met criteria	Met criteria	Met criteria
	B/Brisbane/60/2008	Met criteria	Met criteria	Met criteria	Did not meet criteria
	B/Brisbane/3/2007	Met criteria	Met criteria	Met criteria	Met criteria
Spain	A/California/7/2009 (H1N1)	Met criteria	Did not meet criteria	Met criteria	Met criteria
	A/Victoria/210/2009 (H3N2)	Met criteria	Met criteria	Met criteria	Met criteria
	B/Brisbane/60/2008	Met criteria	Met criteria	Met criteria	Did not meet criteria
	B/Brisbane/3/2007	Met criteria	Met criteria	Met criteria	Met criteria
Korea	A/California/7/2009 (H1N1)	Met criteria	Met criteria	Met criteria	Met criteria
	A/Victoria/210/2009 (H3N2)	Met criteria	Met criteria	Met criteria	Met criteria
	B/Brisbane/60/2008	Met criteria	Met criteria	Met criteria	Did not meet criteria

Country	Strain	Non-Inferiority by GMT	Non-Inferiority by SCR	Superiority by GMT	Superiority by SCR
	B/Brisbane/3/2007	Met criteria	Met criteria	Met criteria	Met criteria
Romania	A/California/7/2009 (H1N1)	Met criteria	Met criteria	Met criteria	Met criteria
	A/Victoria/210/2009 (H3N2)	Met criteria	Met criteria	Met criteria	Met criteria
	B/Brisbane/60/2008	Met criteria	Met criteria	Met criteria	Met criteria
	B/Brisbane/3/2007	Met criteria	Met criteria	Met criteria	Met criteria
Taiwan	A/California/7/2009 (H1N1)		Met criteria	Met criteria	Met criteria
	A/Victoria/210/2009 (H3N2)	Did not meet criteria		Met criteria	Met criteria
	B/Brisbane/60/2008	Met criteria	Did not meet criteria	Met criteria	Did not meet criteria
	B/Brisbane/3/2007	Met criteria	Did not meet criteria	Met criteria	Met criteria

Source: BLA 125127/ SN 513, CSR D-QIV 008, AAR annex

Reviewer comment: The study was not powered to look specifically at the results by country of origin. For the site in the US, 589 subjects received QIV, 198 TIV-1 and 183 TIV-2. For the B/Brisbane/3/2007 strain (from Yamagata lineage) the upper bound of the 95% CI for the difference in seroconversion rate for non-inferiority with the trivalent vaccine was 10.67 (did not meet criteria of ≤10). In addition for the B/Brisbane/60/2008 strain (from the Victoria lineage) for superiority in terms of SCR compared to the trivalent vaccine that did not contain the strain, the lower bound of the 95% CI was -1.46 (did not meet criteria of ≥ 0).

By Previous vaccination:
Criteria were met for non-inferiority and superiority in terms of GMT and SCR for both subjects with and without of prior influenza vaccination in the previous three years.

By sex:
In both males and female criteria was met for non-inferiority and superiority in terms of GMT and SCR.

By ethnicity:
In both White/Caucasian and non-White Caucasians criteria was met for non-inferiority and superiority in terms of GMT and SCR.

Reviewer comment: The subgroups of prior vaccination, gender and ethnicity in this study met the criteria for non-inferiority and superiority. There were no substantial differences between any of the subgroups analyzed.

6.1.12 Safety Analyses

6.1.12.1 Methods

Please see section 6.1.7 for information regarding safety monitoring. Safety was assessed by collection of information for:

- solicited adverse reactions for seven Days post-vaccination;
- unsolicited adverse events for 21 Days post-vaccination; and
- serious adverse events, withdrawals due to AEs, medically attended visits, potential immune mediated disease and pregnancies for the duration of study participation.

Information on concomitant medication use for adverse events was also collected. The analysis of safety was performed on the Total Vaccinated Cohort.

6.1.12.2 Overview of Adverse Events

A total of 3036 D-QIV subjects, 1010 TIV-1 subjects and 610 TIV-2 subjects were included in the analysis of safety. The overall incidence of subjects reporting any adverse event was 49.5% in the D-QIV group, 51.6% in the TIV-1 group and 48.2% in the TIV-2 groups. The incidence of general solicited adverse reactions was similar in each arm (34.5% in D-QIV arm, 36.2% in TIV-1 arm and 33.3% in TIV-2 arm). There were more local solicited adverse reactions in the D-QIV and TIV-1 arms compared to the TIV-2 group (37% in D-QIV group, 37.4% in TIV-1 group and 32% in TIV-2 arm). The overall incidence of subjects with Grade 3 solicited adverse reactions was the same in each arm: 2.6%; the incidence of Grade 3 general solicited adverse reactions and with Grade 3 local solicited adverse reactions were similar in each arm (general : 2% D-QIV, 1.8% TIV-1 and 2% TIV-2 and local: 0.8% D-QIV, 1.2% TIV-1 and 0.1% TIV-2.

Incidence of AEs was analyzed by age strata. The results are shown in the table below

Table 12: D-QIV 008- Percent Incidence and Nature of Adverse Reactions (Solicited and Unsolicited) Reported During the 7 Day Post Vaccine Period by Age Strata (Total Vaccinated Cohort)

Group	Age strata	General symptoms	Grade 3 general symptoms	Local symptoms	Grade 3 local symptoms
D-QIV N= 3036	All Subjects	34.5	2	37	0.8
	18-64	44.4	2.4	51.3	1.4
	65 +	24.7	1.6	22.6	0.3
	18-74	36.6	2.1	40	0.9
	75+	23.2	1.5	20.3	0.2
TIV-1 N= 1010	All Subjects	36.2	1.8	37.4	1.2
	18-64	45.8	2.4	52	0.8
	65 +	26.6	1.2	22.8	0.1
	18-74	37.7	1.8	41.7	1.2
	75+	28.5	1.9	14.6	1.3
TIV-2 N= 610	All Subjects	33.3	2	32	0.5
	18-64	38.2	2	46.8	0.2
	65 +	28.5	1.9	17.5	0
	18-74	34.2	2.1	34	0.6
	75+	28.1	1.1	18	0

Source: BLA 125127/ SN 513, CSR D-QIV 008, Supplement 65-72, page 246-249

Reviewer's comment: Both general and solicited adverse reactions were reported more frequently in the younger age strata, and the rate of solicited adverse reactions was lowest for subjects over 75 years of age (Table 13, 14). The difference was more marked in comparison of rates of local solicited adverse reactions than in rates of general solicited adverse reactions. The lower rates in older subjects are likely to be due to decreased reactogenicity associated with immunosenescence. Grade 3 AEs were uncommon.

The incidence of solicited adverse reactions was analyzed by gender. For all vaccine arms, a higher rate of any solicited adverse reaction was noted in females compared to males (49.3% in D-QIV versus 35.8% for males, 50.4% in TIV-1 versus 39.2% for males, and 40.55 in TIV-1 versus 39.7% in TIV-2). The rate of Grade 3 solicited adverse reactions were uncommon in both genders but slightly higher in females: 2.3% for females and 0.7% for males in D-QIV group; 2% for females and 2.4% in males for TIV-1 group and 1.5% for females and 3% for males in TIV-2 group.

Reviewer's comment: There were no specific local or solicited adverse reactions that were more prevalent in males versus females; there was a general increase in all adverse reactions for females. The reason for this is unclear to this reviewer, although this data is not inconsistent with what is reported in the literature. It has been suggested that sex-differences in local reactions following vaccination is multifactorial and include differences in type III reactions, hormonal factors as well as changes in vascular permeability between males and females (Sex differences in injection site reactions with human vaccines.Cook IF. Hum Vaccin. 2009 Jul;5(7):441-9).

Local solicited adverse reactions
Information on local solicited AEs was collected from Day 0 to Day 7. The incidence of local solicited AEs and the percentage of Grade 3 local solicited AEs are shown in the table below.

Table 13: D-QIV 008 Percentage of Subjects with Local Solicited Adverse Reactions and Grade 3 Local Adverse Reactions by Age Strata (Total Vaccinated Cohort)

		D-QIV (N=3015)	**TIV-1 (N=1003)**	**TIV-2 (N=607)**
Pain	All Subjects with Pain	36.4	36.8	31.3
	18-64 (N=1510)	50.9	50.6	45.5
	65 + (N=499)	21.7	22.8	17.3
	18-74 (N=2549)	39.6	40.9	33.7
	75+ (N=156)	18.7	14.7	17.2
	All Subjects with Grade 3 Pain	0.8	1.2	0.5
	18-64	1.4	1.8	1
	65 +	0.2	0.6	0
	18-74	0.9	1.2	0.6
	75+	0.2	1.3	0
Redness	All Subjects with Redness	1.9	1.7	2
	18-64	2.2	2.4	3.7
	65 +	1.7	1	0.3

	18-74	2	2	2.1
	75+	1.3	0	1.1
	All Subjects with Grade 3 Redness	0	0	0
	18-64	0	0	0
	65 +	0.1	0	0
	18-74	0	0	0
	75+	0	0	0
Swelling	All Subjects with Swelling	2.1	2.1	1.3
	18-64	2.8	3.4	1.7
	65 +	1.3	0.8	1
	18-74	2.3	2.5	1.3
	75+	0.6	0	1.1
	All Subjects with Grade 3 Swelling	0	0	0
	18-64	0	0	0
	65 +	0	0	0
	18-74	0	0	0
	75+	0	0	0

Source: BLA 125127/ SN 513, CSR D-QIV 008, Supplement 80-83, page 253-256

As shown in the table above, the most common local solicited adverse reaction was pain which was reported at a similar rate in the three vaccine groups. The percentage of subjects with swelling and redness was also similar in all three groups and in all age strata. There were almost no Grade 3 redness or swelling in any of the groups regardless of age strata.

Of local solicited adverse reactions by gender, injection site pain was reported more frequently in females in all treatment groups. In addition the percentage of subjects with injection site redness and swelling was higher in females than males in the D-QIV and TIV-2.

Reviewer comment: Pain was the most commonly reported local AE; however, only a small percentage (≤1.8%) of pain was severe. The rate of subjects with local solicited adverse reactions was higher in females than males. The reason for this difference is unclear, but one could theorize that females had more local reactions due to lower body mass indices and smaller arm size.

The maximum intensity of the local AEs was compared by study Day. The number of subjects with any of the individual reactogenicity events peaked on Days 2 and 3.

General solicited adverse reactions
Information on general solicited adverse reactions was also collected for the Day of vaccination and the seven subsequent Days. The results are shown in the table below.

Table 14 : D-QIV 008 Percentage of Subjects with General Solicited Adverse Reactions and Grade 3 General Adverse Reactions by Age Strata (Total Vaccinated Cohort)

			D-QIV (N=3015)	**TIV-1 (N=1003)**	**TIV-2 (N=607)**
Fatigue	All	All Subjects	15.8	18.4	14.8
		18-64 (N=1510)	21.4	24.2	17.9
		65 + (N=499)	10.2	12.6	11.8

		18-74 (N=2549)	17	19.4	15.2
		75+ (N=156)	9.7	13.5	12.6
	Grade 3	All Subjects with Grade 3	0.7	0.6	0.5
		18-64	0.9	1	0.3
		65 +	0.5	0.2	0.7
		18-74	0.8	0.7	0.6
		75+	0.2	0	0
Gastrointestinal	All	All Subjects	6.5	6.5	5.9
		18-64	7.6	7.3	6.3
		65 +	5.5	5.6	5.6
		18-74	6.8	5.8	6
		75+	5.2	10.3	5.7
	Grade 3	All Subjects with Grade 3	0.4	0.2	0.3
		18-64	0.3	0.2	0.3
		65 +	0.5	0.2	0.3
		18-74	0.4	0.2	0.4
		75+	0.2	0	0
Headache	All	All subjects	15.9	16.4	13.2
		18-64	22	21.8	14.6
		65 +	9.8	10.8	11.8
		18-74	17.2	17.6	12.7
		75+	9	9.6	16.1
	Grade 3	All subjects with Grade 3	0.9	0.8	0.7
		18-64	1.3	14.3	1
		65 +	0.4	0.2	0.3
		18-74	1	0.9	0.8
		75+	0.2	0	0
Joint pain	All	All Subjects	8.4	10.4	9.4
		18-64	9	11.1	9
		65 +	7.9	9.6	9.8
		18-74	8.5	10.2	9.4
		75+	7.9	11.5	9.2
	Grade 3	All Subjects with Grade 3	0.5	0.7	0.3
		18-64	0.4	0.8	0
		65 +	0.5	0.6	0.7
		18-74	0.4	0.6	0
		75+	0.9	1.3	1.1
Muscle ache	All	All Subjects	16.4	19.4	16.1
		18-64	22.8	25.8	20.6
		65 +	8.5	13	11.8
		18-74	17.7	20.4	16.7
		75+	9	14.1	12.6
	Grade 3	All Subjects with Grade 3	0.5	0.8	0.5
		18-64	0.7	1.0	0.3
		65 +	0.1	0.6	0.7
		18-74	0.5	0.7	0.6
		75+	0.2	1.3	0

Shivering	All	All Subjects	4.2	5	4.3
		18-64	4.2	5.6	5
		65 +	3.1	4.4	3.6
		18-74	4.3	4.4	4.2
		75+	3.2	8.3	4.6
	Grade 3	All Subjects with Grade 3	0.4	0.3	0.2
		18-64	0.4	0.4	0
		65 +	0.1	0.2	0.3
		18-74	0.4	0.2	0.2
		75+	0.2	0.6	0
Fever	All	All Subjects	0.6	1.2	1.5
		18-64	2.1	1.4	1.7
		65 +	1.1	1	1.3
		18-74	1.7	1.2	1.7
		75+	1.3	1.3	0
	Grade 3	All Subjects with Grade 3	0	0	0
		18-64	0	0	0
		65 +	0	0	0
		18-74	0	0	0
		75+	0	0	0

Source: BLA 125127/ SN 513, CSR D-QIV 008, Table 50, supplement 90,93, 96, page 105, 264-274

Fatigue, headache and muscle aches were the most commonly reported general solicited adverse reactions. Grade 3 general solicited adverse reactions were reported by less than 1 % in all vaccine arms. Fever was uncommon and reported in less than 2% in all vaccine arms, no Grade 3 (>39.0°C) fever was reported.

Reviewer comment: Muscle aches was the most commonly reported general solicited adverse reaction, followed by fatigue and headache. However, severe general solicited adverse reactions were uncommon with only four subjects with emergency department visits due to a general solicited adverse reaction.

The incidence of each general solicited reactogenicity event was highest on Day 3 post-vaccination.

Reviewer comment: Because the information on general solicited adverse events was collected from Days 0-7 only, the maximum intensity of these reactions was captured.

General solicited adverse reactions were analyzed by gender. In the D-QIV and TIV-1 arms, females reported more general solicited adverse reactions than males primarily due to higher rates of headaches and muscle aches.

Reviewer comment: The reason for the higher percentage of females with any general solicited adverse reaction is unclear. Twice as many females than males experienced headaches and between 3-5% more females than males experiences fatigue and muscle aches.

Unsolicited adverse events
Unsolicited adverse events were collected for 21 Days post-vaccination in all three study arms.

The percentage of subjects reporting unsolicited adverse events was similar in the D-QIV (12.5%, TIV-1 (14.7%) and TIV-2 (15.1%) arms. Only three individual unsolicited AEs were reported in more than 1% of subjects in either study arm; these were reported in similar percentages in all arms; nasopharyngitis (1.4% in D-QIV arm, 1.7% in TIV-1 arm and 1.5% in TIV-2 arm); cough (1.2% in D-QIV arm, 1.4% in TIV-1 arm and 1.5% in TIV-2 arm); and oropharyngeal pain (0.9% in D-QIV arm, 1.4% in TIV-1 arm and 1% in TIV-2 arm).

Information on medically attended visits was collected for the entire study period for subjects in the D-QIV and TIV-1 arms and for the 21 Days post-vaccination in the TIV-2 arm. During the 21 Day post vaccination period for all three arms, the percentage of subjects who had at least one unsolicited adverse events with medically attended visit was similar: 6.4% in D-QIV group, 5.9% in TIV-1 group and 7.7% in TIV-2 group. During the entire study period 22.7% subjects in D-QIV group and 21.4% subjects in TIV-1 group had events with medically attended visit. Upper respiratory infection in TIV-1 arm was the only medically attended AE reported in more than 1 % (1.2%).

Grade 3 unsolicited AEs were uncommon and reported in similar percentages in each study arm: 1.3% in D-QIV, 0.7% in TIV-1 and 0.3% in TIV-2. No grade 3 unsolicited AEs were reported in more than 1 % of subjects in either arm.

Reviewer comment: The percentages of subjects with unsolicited AEs and with medically attended AEs were similar between the three study arms. In addition, the most common AEs reported were consistent with illnesses commonly reported in adults. Grade 3 unsolicited adverse events were not commonly reported.

Vaccine Safety by Lot
The number and percentage of solicited adverse reactions of the three separate D-QIV lots are shown in the table below.

Table 15 : D-QIV 008- Percent Incidence and Nature of Symptoms (Solicited and Unsolicited Reported During the 7 Day Post Vaccine Period by Vaccine Lots (Total Vaccinated Cohort)

Group	Any symptoms	General symptoms	Local symptoms	Grade 3 symptoms	Grade 3 general symptoms	Grade 3 local symptoms
D-QIV-1 N= 1012	50.1	34.7	38.2	2.6	1.7	1.3
D-QIV-2 N= 1013	48.5	34.2	36.2	2.9	2.3	0.7
D-QIV-3 N= 1011	50	34.7	36.5	2.4	2.2	0.5

Source: BLA 125127/ SN 513, CSR D-QIV 008, Supplement 61, 63 page 245, 244

Reviewer comment: There were no safety signals noted for an individual lot. As shown in the preceding table, there was no significant difference in the percentage of subjects with adverse reactions or severe solicited adverse reactions amongst the three lots.

6.1.12.3 Deaths

There were 9 deaths in the D-QIV arm, 3 in the TIV-1 arm, and none in the TIV-2 arm;
In the D-QIV arm:

- Subject 461, an 85 year old male with significant past medical history including hypertension, Parkinson's disease, and gastric ulcer received D-QIV on ------(b)(6)------- and died of sudden death 3 months later at home.
- Subject 2140 an 85 year old female with a history of congestive heart failure and atrial fibrillation, received D-QIV on -------(b)(6)-------- and died of myocardial infarction 6 months later.
- Subject 3023: an 84 year old female with history of mesenterial infarction, chronic bronchitis, arrhythmia, and pulmonary emboli, received D-QIV on November 4th 2010, presented to the hospital with erysipelas on ------(b)(6)-------, and died suddenly 2 Days later.
- Subject 4373: an 81 year old female with history of heart failure received D-QIV on ------(b)(6)------ and died of cardiopulmonary failure 3 months later.
- Subject 6609: a 71 year old male with history of pulmonary hypertension received D-- QIV on ------(b)(6)-------, and died of pulmonary hypertension 5 months later.
- Subject 7347: a 71 year old female with history of hypertriglyceridemia received D-QIV on ------(b)(6)------- and died of myocardial infarction 1 month later.
- Subject 987: a 68 year old female with history of liver cirrhosis received D-QIV on ------(b)(6)------ and died of hepatic coma 3 months later.
- Subject 5468: a 73 year old male with history of hypertension, ventricular hypertrophy and hypercholesterolemia received D-QIV on ------(b)(6)------- and died of a stroke 6 months later.
- Subject 6594: a 71 year old female received D-QIV on ------(b)(6)-------, and died 2 months later of small cell lung cancer.

In the TIV-1 arm:
- Subject 3735: an 86 year old male with history of hypertension and ischemic heart disease received TIV-1 on ------(b)(6)------- and died of cardiac arrest 2 months later
- Subject 4362: an 69 year old male with history of atrial fibrillation, hypertension and heart failure received TIV-1 on ------(b)(6)------- and died of cardio-respiratory arrest 3.5 months after
- Subject 5518: a 69 year old male with history of ischemic heart disease received TIV-1 on ------(b)(6)------- and died of a cardiac disorder 2 weeks later at home, necropsy report is pending.

Reviewer comment: All of the deaths were reported in subjects 68 years of age or older. Only two deaths were reported within one month of vaccination: one subject due to myocardial infarction and the other due to cardiac disease. Both subjects had chronic diseases predisposing the subjects to heart disease. The causes of death were consistent with serious illnesses reported in an elderly population. The number of deaths in each study arm was consistent with the randomization (3:1:1) and the length of follow-up (only 21 Days post-vaccination in the TIV-2 arm compared to 180 Days in the other two arms). In the opinion of the investigators and of this reviewer, none of the deaths appear to be related to study vaccine.

6.1.12.4 Nonfatal Serious Adverse Events

Serious adverse events
One hundred and twenty seven serious AEs were reported in 97 subjects for the entire study period: 0.5% in D-QIV arm, 0.6% in TIV-1 arm and 0.2% in TIV-2 arm. The number of SAEs was similar when analyzed by gender: 63 serious AEs occurred in males and 64 in females. Serious AEs that were reported in more than one subject are shown in the table below.

Table 16: D D-QIV-008 - Number of Subjects with Serious Adverse Events which Were Reported in Two or More Subjects in Either Treatment Arm

Serious Adverse Event	D-QIV	TIV-1	TIV-2
Cardiac failure	2	0	0
Cardiac Failure congestive	3	0	0
Myocardial Infarction	5	1	0
Gastric ulcer hemorrhage	2	0	0
Cholilethiasis	2	0	0
Pneumonia	3	2	0
Respiratory Tract Infection	2	0	0
Urinary Tract Infection	2	0	0
Invertebral disc protusion	2	0	0
Gastric adenoma	3	0	0
Cerebrovascular accident	5	2	0
Nephrolithiasis	0	2	0

Source: BLA 125127/ SN 513, CSR D-QIV 008, Table 65 page 161

The most frequently reported SAEs were cerebral vascular accident (N=7) myocardial infarction (N=6), and pneumonia (N=5).

Reviewer comment: The incidence of individual serious AEs was low and was similar between the three treatment arms. There was no difference in rate of SAEs by gender. There did not appear to be an increase in any individual SAE or related SAEs in this study.

6.1.12.5 Adverse Events of Special Interest (AESI)

Adverse Events of Special Interest or AESI included:
Neuroinflammatory disorders: optic neuritis, cranial nerve disorders (including Bell's palsy), multiple sclerosis, demyelinating disease, transverse myelitis, GBS, myasthenia gravis, encephalitis, neuritis.
Musculoskeletal disorders: systemic lupus erythematosus, cutaneous lupus, Sjögren's syndrome, scleroderma, dermatomyositis, polymyositis, rheumatoid arthritis and juvenile rheumatoid arthritis, polymyalgia rheumatica or temporal arteritis, reactive arthritis, psoriatic arthropathy, ankylosing spondylitis, undifferentiated spondyloarthropathy.
Gastrointestinal disorders: Crohn's disease, ulcerative colitis or proctitis, celiac disease.
Metabolic diseases: autoimmune thyroiditis, Grave's or Basedow's disease, Hashimoto thyroiditis, insulin-dependent diabetes mellitus (IDDM), Addison's disease.
Skin disorders: psoriasis, vitiligo, Raynaud's phenomenon, erythema nodosum, autoimmune bullous skin diseases.
Others: autoimmune hemolytic anemia, thrombocytopenias, antiphospholipid syndrome, vasculitis, pernicious anemia, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune glomerulonephritis, autoimmune uveitis, autoimmune myocarditis/cardiomyopathy, sarcoidosis, Stevens-Johnson syndrome, Behçet's syndrome

Two subjects reported potential immune mediated disease. Additional information from the Case Report Forms is included below.
Subject 8312: a 43 year old female who received D-QIV on was diagnosed with multiple sclerosis 3 months later
Subject 5196: a 63 year old female who received TIV-1, developed facial nerve paralysis 4 months later, and recovered within 10 Days.

6.1.12.6 Clinical Test Results

No safety laboratory tests were obtained in this study.

Pregnancy
Five pregnancies (3 in the D-QIV arm and 2 in the TIV-1 arm) were reported during the study. All subjects were exposed to vaccine before conception, and all pregnancies were recognized at 4-6 months after vaccine administration. The outcome was unknown for four of the five pregnancies at the time that the clinical study report was written. The other pregnancy resulted in a "live male neonate" born at 36 weeks gestation. .

6.1.12.7 Dropouts and/or Discontinuations

Fourteen subjects withdrew from the study prematurely because of an adverse event. Twelve of these withdrew due to death,, one due to rectal carcinoma, and one due to sinusitis.

6.1.13 Comments and Conclusions

The results of Study D-QIV 008 provide the primary basis for demonstration of immunogenicity and safety of Fluarix Quadrivalent in adults. In this study, all three co-primary immunogenicity objectives were met. Lot consistency was also demonstrated, non-inferior immunogenicity of D-QIV was demonstrated for all 4 strains, and superior immunogenicity of D-QIV was demonstrated for the B strain not present in Fluarix.

The most common adverse events associated with D-QIV in this study were reactogenicity events, particularly pain at the injection site, fatigue, and headache. The majority of these solicited adverse reactions were mild or moderate in intensity. There was no increase in the incidence of unsolicited individual AEs or AEs with a specific organ system. Finally, serious adverse events were uncommon. In this reviewer judgment, there were no safety signals identified in the review of this study.

6.2 D-QIV 003

A Phase III, double-blinded, randomized study to evaluate the immunogenicity and safety of quadrivalent influenza vaccine compared to Fluarix administered intramuscularly in children 3 to 17 years and to describe the safety and immunogenicity of quadrivalent influenza vaccine in children aged 6-35 months

6.2.1 Objectives

The primary objective of Study D-QIV 003 was to demonstrate the immunological non-inferiority, as measured by GMTs and seroconversion rate, of D-QIV compared to TIV-1 and TIV-2 in children 3-17 years.

The secondary objectives were:
- To demonstrate the immunological superiority of D-QIV versus TIV-1 and TIV-2 for the influenza B strain not contained in each formulation,
- To describe the immunogenicity of D-QIV versus TIV-1 and TIV-2 post-vaccination by GMT, seroconversion rate, mean geometric increase, and percentage of subjects with HI titers $\geq$ 1:40 post-vaccination in all subjects and in a subset of subjects 6-35 months of age, and
- To compare safety of D-QIV, TIV-1 and TIV-2 in subjects 6-35 months

6.2.2 Design Overview

D-QIV--003 was a Phase III, randomized, double-blinded, multi-center study in three parallel groups. Subjects were stratified by age with a ratio of 2:1 for children 3-8 years and 9-17 years. A total of 2750 subjects ages 3-17 years old were enrolled, randomized in a 1:1:1 ratio to receive Flu D-QIV, TIV and TIV-2, and were studied in an observer-blind design. An additional 277 subjects aged 6-35 months were enrolled and received D-QIV in an open label design. Minimization factors for treatment allocation included previous H1N1 vaccination and priming status. Primed subjects 6 months-8 years, defined as those who had received at least one dose of an influenza A H1N1 2009 monovalent vaccine in the last season AND has received two doses of seasonal influenza immunizations separated by at least one month during the last season, received one dose of the study vaccine. Subjects 6 months-8 years who were unprimed, defined as subjects who had not received influenza A H1N1 2009 monovalent vaccine in the last season, had not received any season influenza immunization in the past, or had received only one dose of vaccine for the first time in the last season, received two doses one at Day 0 and one at Day 28. Subjects 9-17 years received a single dose of study vaccine regardless of vaccination history.

Primed subjects were vaccinated with study vaccine at the first study visit and returned 28 Days later for the post-immunization blood draw and review of adverse events. Unprimed subjects received study vaccine at first study visit and a second dose 28 Days later; blood samples for antibody titers were collected at baseline and on Days 28 and 56.

6.2.3 Population

The study enrolled healthy children age 6 months- 17 years of age at the time of vaccination. Subjects were excluded if they had received seasonal or pandemic influenza vaccine in the previous 6 months. Individuals were excluded if they had a history of hypersensitivity to a previous dose of influenza vaccine or a history of allergy or reactions likely to be exacerbated by any vaccine component. Individuals were also excluded for acute disease or fever at the time of enrollment, for a history of Guillain Barré syndrome within six weeks of enrollment, for history of seizures (except history of a single febrile seizure), for coagulation disorder, immunodeficiency, or for history of chronic disorder (pulmonary, cardiovascular, hepatic or renal).

6.2.4 Study Treatments or Agents Mandated by the Protocol

Unprimed subjects in the 3-8 year age cohort received two doses of study vaccine administered 28 Days apart. Primed children from 3 – 8 years of age received a single dose of study vaccine. All subjects 9-17 years of age received a single dose of study vaccine. All subjects in the open label 6 months to 35 months cohort received two doses of study vaccine administered 28 Days apart.

TIV-1 (Fluarix) contained the three influenza strains recommended for the 2010-2011 influenza season in the Northern Hemisphere; the influenza B strain recommended was from the Victoria lineage. TIV-2 contained the two recommended influenza A subtypes and a influenza B strain from the Yamagata lineage. The D-QIV formulation included both influenza A and influenza B strains. For a complete descriptions of the study vaccines, see Section 6.1.4 for details of strain and antigens for TIV-1, TIV-2 and D-QIV.

6.2.6 Sites and Centers

The study was conducted under IND 14473 in 55 centers in five countries: Czech Republic, France, Germany, Philippines and USA

6.2.7 Surveillance/Monitoring

Unprimed subjects younger than 9 years of age were seen in the study clinic on Days 0, 28, and 56. Primed subjects younger than 9 years of age and all subjects 9 to 17 years of age were seen in the study clinic on Days 0 and 28. All subjects were contacted by telephone for safety follow-up on Day 180.

Medical history was obtained prior to vaccination on Day 0. A physical examination was performed prior to vaccination on Day 0 and was repeated if deemed necessary by the investigator at subsequent visits. Vital signs (heart rate and respiratory rate) and body temperature was measured prior to each vaccination. A urine pregnancy test was obtained for all females of childbearing potential prior to vaccination; the test must have been negative for the subject to be vaccinated.

Subjects were observed for 30 minutes after vaccination. Diary cards were distributed to the subjects' parent or legally acceptable representative after vaccination.

Information on solicited adverse reactions was collected for seven Days after vaccination (Day of vaccination and subsequent six Days). The solicited local adverse reactions to be followed were pain, redness, and swelling at the injection site. Pain in children younger than 6 years of age will be graded in intensity as none (Grade 0), mild (minor reaction to touch, Grade 1), moderate (cries / protests on touch, Grade 2), or severe (cries when limb is moved / spontaneously painful, Grade 3). Pain in children 6 years of age and older were graded as none (Grade 0), mild (not interfering with normal activity, Grade 1), moderate (painful when limb is moved and interferes with daily activity, Grade 2), or severe (significant pain at rest, prevents normal activity, Grade 3). The greatest surface diameter of redness and swelling was recorded in millimeters.

The solicited general adverse reactions followed in infants and toddlers (subjects younger than 5 years of age) were drowsiness, fever, irritability/fussiness, and loss of appetite. The solicited general adverse reactions followed in children 5 years of age and older were fatigue, fever, headache, joint pain, muscle aches (widespread or general), shivering, and gastrointestinal symptoms (nausea, vomiting, diarrhea, and/or abdominal pain). All solicited systemic adverse reactions were graded in intensity as none (Grade 0), mild (present but no effect on normal daily activity and easily tolerated, Grade 1), moderate (interferes with normal activity, Grade 2) and severe (prevents normal activity, Grade 3). In addition, fussiness in children younger than 5 years of age was also graded in intensity as none (Grade 0), mild (crying more than usual, Grade 1), moderate (crying more than usual and interferes with daily activity, Grade 2), or severe (crying that cannot be comforted, Grade 3). Loss of appetite was graded as none (Grade 0), mild (eating less than usual, Grade 1), moderate (eating less than usual and interferes with daily activity, Grade 2), or severe (not eating at all, Grade 3). Fever was defined as rectal temperature ≥ 38.0° C (100.4° F), axillary temperature ≥ 37.5° C (99.5° F), or oral temperature ≥ 37.5° C (99.5° F). Grade 3 fever was defined as axillary temperature > 39.0° C (102.2° F).

Information on unsolicited adverse events (AEs) was collected for 28 Days after vaccination. Information on medically attended AEs, potential immune mediated

diseases, and serious AEs were collected during the entire study period. Information on all concomitant medications and vaccines received by subjects, except vitamins and dietary supplements, were collected during the 28 Days post-vaccination.

6.2.8 Endpoints and Criteria for Study Success

The primary endpoint was serum HI antibody titers. The antibody titers were used to analyze non-inferiority and superiority using geometric mean antibody titers (GMTs) against the four influenza vaccine strains at Day 0 and Day 28 and seroconversion rates (defined as the percentage of subjects who had either a pre-vaccination HI titer <1:10 and post-vaccination HI titer ≥ 1:40 or a pre-vaccination HI titer > 1:10 with at least a four fold increase in post-vaccination titer) at Day 28.

Secondary endpoints for immunogenicity included the percentage of subjects with HI titers ≥ 1:40 on Days 0, 28, and 56, GMTs of HI antibody titers on Days 0, 28, and 56, seroconversion rates on Day 28, and 56and geometric mean of the within subject ratios of the post-vaccination reciprocal HI titers on Days 28 and 56. Secondary endpoints for safety included solicited local and general AEs during a 7 Day follow up period after vaccination, unsolicited AEs for 28 Days after vaccination and SAEs for the entire study period.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Treatment allocation at each study site was performed using an internet randomization system (SBIR). Within each age strata (3-8 years and 9-17 years) the randomization algorithm used a minimization procedure accounting for the country, study center, previous influenza vaccination history and priming status.

The comparison of D-QIV, TIV-1 and TIV-2 arms in children 3-17 years of age were conducted in a double-blinded fashion. Subjects 6-35 months received open label D-QIV. The laboratory in charge of antibody testing was blinded to the treatment.

The primary objective was to determine the non-inferiority of D-QIV versus TIV 1 and TIV 2; the criteria for successfully meeting this objective were 1) the upper limit of the two-sided 95% CI of the GMT ratio had to be less than 1.5 for each strain and 2) the absolute difference in seroconversion had to be less than 10% for each of the three strains in each TIV vaccine.

Descriptive statistical parameters were calculated for the safety data. The sponsor states that there is 90% power to detect a difference in the incidence of adverse events between study groups.

The study populations were as follows:
The Total Vaccinated Cohort included all vaccinated subjects for whom data were available for review.
The Total Vaccinated Cohort for safety included all subjects with at least one documented vaccine administration.
The Total Vaccinated Cohort for analysis of immunogenicity included vaccinated subjects for whom data concerning immunogenicity endpoint measures were available.
The ATP cohort for analysis of safety included all subjects who were vaccinated according to randomized assignment, for whom the administration site of vaccine was known, who had not received a vaccine forbidden in the protocol, for whom the randomization code was not broken and who had sufficient safety data available.

The ATP cohort for analysis of immunogenicity included all subjects who met all eligibility criteria, complied with the study protocol, met no elimination criteria, did not receive a product leading to exclusion, did not present with a medical condition leading to exclusion that could alter their immune response (i.e., varicella) and for whom immunogenicity measurements were available.

6.2.10 Study Population and Disposition

The study was conducted in 55 centers in five countries: Czech Republic, France, Germany, Philippines and USA. The first study subject was enrolled on October 4, 2010. The last study visit was June 15, 2011.

6.2.10.1 Populations Enrolled/Analyzed

A total of 3015 subjects were vaccinated in this study: 915 in the D-QIV group, 912 in the TIV-1 group and 911 in the TIV-2 group. An additional 277 were vaccinated in the open label D-QIV group for infants aged 6-35 months (D-QIV-Y).

6.2.10.1.1 Demographics

For subjects 3-17 years old:
The mean age of subjects in all three arms was 7.8 years; 48% of subjects were females. Most subjects were White Caucasians (54% in the D-QIV arm, 52% in the TIV-1 arm and 53% in the TIV-2 arm), 29% in all three arms were Asians of south east heritage, and 12% were African American.

Most subjects had not been previously vaccinated against influenza; 37% in both the D-QIV and TIV-1 arm and 35% in the TIV-2 arms had been vaccinated against influenza within the previous three years.

Reviewer comment: The baseline demographic characteristics were similar between the three study arms.

The demographic profiles in the ATP cohort for immunogenicity were comparable to those of the Total Vaccinated Cohort.

For subjects 6-35 months:
The mean age was 22 months, 43% of subjects were females and the population was predominantly White Caucasian (70%). In this cohort, 15% of subjects were administered a seasonal influenza vaccine in the three previous seasons.

6.2.10.1.3 Subject Disposition

The number of subjects vaccinated, completing or withdrawing from the study is shown in the following table.

Table 17: D-QIV-003 – Study Subject Disposition

	D-QIV	TIV-1	TIV-2	D-QIV-Y	Total
Number of subjects vaccinated	915	912	911	277	3015
Number of subjects completing study	891	880	886	876	2933
Number of subjects discontinuing prematurely	24	32	25	1	82
Reasons for premature discontinuation					
Lost to follow-up	15	27	21	1	64

Consent withdrawn	5	1	4	0	10
Serious adverse event	1	1	0	0	2
Non-serious adverse event	0	1	0	0	1

Source: BLA 125127/ SN 513, CSR D-QIV 003, Table 20, page 111

As shown in the table above, the majority of subjects (97%) who were vaccinated completed the study. The main reason for premature study discontinuation was loss to follow-up. Three subjects discontinued the study prematurely due to an adverse event: 2 in the D-QIV arm and one in the TIV-1 arm. Please see a discussion of these three subjects later in this review.

Reviewer comment: There were more premature study discontinuations in the TIV-1 arm than in the other arms. Most were due to loss to follow-up. However, the number of discontinuations was small, and the majority was observed in the control arm. This suggests that the study was well conducted.

Of the 3015 subjects in the Total Vaccinated Cohort, twenty one were excluded from the ATP safety cohort. An additional 370 subjects were excluded from the ATP immunogenicity cohort. The reasons for exclusion are shown in the following table.

Table 18: D-QIV-003 – Reasons for Exclusion from the ATP Safety and Immunogenicity Cohort

	D-QIV	**TIV-1**	**TIV-2**	**D-QIV-Y**	**Total**
Total Vaccinated Cohort	915	912	904	276	3015
ATP cohort for safety	905	909	904	276	2994
Randomization failure	5	2	3	0	10
Vaccine not administered according to protocol	5	1	4	1	11
ATP Immunogenicity Cohort	791	819	801	234	2645
Non-compliance with blood sampling schedule	69	59	68	24	220
Serological data missing	25	22	23	10	80
Non-compliance with vaccination schedule	6	4	5	8	22

Source: BLA 125127/ SN 513, CSR D-QIV 003, Table 21, page 112

The majority of subjects were included in the ATP safety cohort (99%). Most (88%) subjects were included in the Immunogenicity cohort, the number of subjects who were excluded and the reasons for exclusion were similar between the four study arms. The main reason for exclusion was non compliance with blood sampling and essential serological data missing. The noncompliance with blood sampling mainly came from one site in the Philippines due to miscalculation of the interval window between visit 2 and 3.

Reviewer comment: A total of 786 subjects were enrolled the Philippines site and a total of 220 or 28% of subjects were excluded from the Total Vaccinated Cohort. The large number of excluded participants could potentially introduce bias in interpretation of the immunogenicity results.

6.2.11.1 Analyses of Primary Endpoint(s)

The primary objective was to assess non-inferiority of D-QIV versus TIV in terms of HI antibody GMTs and seroconversion rates for the three strains that were included in each of TIV-1 and TIV-2 in children 3-17 years. Criteria for successfully meeting this objective were if the upper limited of the two-sided 95% CI for the ratio of GMT of TIV-1 or TIV-2 over D-QIV vaccine did not exceed 1.5 for each strain and if the upper limit of the two-sided 95% CI for the difference in seroconversion rate of TIV 1 or TIV2 minus D-QIV did not exceed 10% for each strain.
The results are shown in the table below.

Table 19: D-QIV-003 – Non-inferiority of D-QIV versus TIV (TIV1 and TIV-2) Using GMTs and Seroconversion Rate at Day 28 After Last Vaccination (ATP Cohort for Immunogenicity)

Vaccine Strain	GMT Ratio TIV/D-QIV		Seroconversion Rate (TIV-D-QIV)	
	Value	UL 95% CI*	Value	UL 95% CI*
A/California (H1N1) **N TIV= 1618** **N D-QIV= 790**	1.06	1.15	0.66	1.86
A/Victoria (H3N2) **N TIV= 1618** **N D-QIV= 790**	0.98	1.05	-1.02	2.86
B/Brisbane (Victoria) **N TIV1= 818** **N D-QIV= 790**	1	1.09	-1.54	2.98
B/Brisbane(Yamagata) **N TIV2= 800** **N D-QIV= 790**	1.09	1.18	-1.78	2.65

*CI = confidence interval
Source: BLA 125127/ SN 513, CSR D-QIV 003, Table 24-29, page 118-120

Criteria for non-inferiority of D-QIV versus TIV in terms of adjusted GMT ratio and seroconversion rates were met for all 4 strains.

Reviewer comment: Non-inferiority of the antibody response to the influenza strains in D-QIV to the corresponding influenza strains in two trivalent formulations was demonstrated. Therefore, the primary endpoint for the study was met.

6.2.11.2 Analyses of Secondary Endpoints

The secondary endpoint included evaluation of the superiority of D-QIV versus TIV-1 and TIV-2 for the cross reactive antibody response to the influenza B strain that was not included in each TIV vaccine in terms of HI antibody GMTs and SCRs. Criteria for successfully meeting this objective were if the lower limit of the two-sided 95% CI on GMT ratio of D-QIV over TIV-1 or D-QIV over TIV-2 was greater than 1 and the lower limit of the two-sided 95% CI for the difference in seroconversion rate was greater than 0. The results are shown in the table below.

Table 20: D-QIV-003 – Superiority of D-QIV versus TIV (TIV1 and TIV-2) in Terms of GMTs at Day 28 After Last Vaccination (ATP Cohort for Immunogenicity)

Vaccine Strain	GMT Ratio D-QIV/TIV		Seroconversion Rate (D-QIV-TIV)	
	Value	LL 95% CI*	Value	LL 95% CI*
B/Brisbane (Victoria) N TIV2= 800 N D-QIV= 790	2.87	2.63	41	35.78
B/Brisbane(Yamagata) N TIV1= 818 N D-QIV= 790	2.55	2.36	35	30.87

*CI = confidence interval
Source: BLA 125127/ SN 513, CSR D-QIV 003, Table 30-33, page 121-122

Criteria for superiority of antibody response to influenza B strains in D-QIV versus the cross reactive antibody response to the influenza B in the TIV s in terms of adjusted GMT ratio and seroconversion rate difference were met for both influenza B strains that were not included in the respective TIV.

Reviewer comment: The antibody response to the influenza B strain included in D-QIV was superior to the cross-reactive antibody response to the influenza B strain from the opposite lineage strain included in the TIV. This demonstrates that antibody response to an influenza B strain is not likely to provide an adequate antibody response to influenza B strains from the opposite lineage, therefore, justifying the inclusion of a second B strain in influenza vaccines.

The secondary endpoints included a description of the immunogenicity of the D-QIV vaccine, TIV-1 and TIV-2 in terms of GMTs and percentage of subjects with HI titers ≥ 1:40 at Days 0 and 21. These results are shown in the following table and include results for the open-label D-QIV arm in subjects 6 to 35 months of age (D-QIV-Y arm).

Table 21: D-QIV 003- Seropositivity Rates (HI Titers ≥ 1:10) , GMTs for HI Antibodies 28 Days after Last Vaccination and HI Titer ≥1:40 (ATP Cohort for Immunogenicity)

			Seropositivity			GMT			HI Titer ≥1:40		
Strain	**Group**	**Timing**	**%**	**LL 95% CI***	**UL 95% CI***	**Value**	**LL 95% CI***	**UL 95% CI***	**%**	**LL 95% CI***	**UL 95% CI***
A/California (H1N1)	D-QIV	Pre	64.7	61.2	68	21.6	19.7	23.7	43.4	39.9	47
		Post	99.9	99.3	100	386.2	357.3	417.4	96.6	95.1	97.7
	TIV-1	Pre	68.9	65.6	70	24.9	22.8	27.3	49.3	45.9	52.8
		Post	99.4	98.6	99.8	433.2	401	468	96.9	95.5	98
	TIV-2	Pre	63.5	60.1	66.8	22.1	20.1	24.2	44.1	40.6	47.6
		Post	99.6	98.9	99.9	422.3	390.5	456.5	97.1	95.7	98.2
	D-QIV Y	Pre	31	25.1	37.4	12.3	10.2	14.8	25.9	20.4	32
		Post	97	93.9	98.8	140	113.7	172.3	79.9	74.2	84.9
A/Victoria/ (H3N2)	D-QIV	Pre	79.6	76.6	82.4	29	26.6	31.6	48.2	44.7	51.8
		Post	99.9	99.3	100	228.8	215	243.4	98	96.7	98.8
	TIV-1	Pre	82.2	79.4	84.7	31.4	28.8	34.2	50.3	46.8	53.8
		Post	99.8	99.1	100	227.3	213.3	242.3	97.8	96.5	98.7
	TIV-2	Pre	79.1	76.1	81.9	31.2	28.6	34.2	51.1	47.6	54.6
		Post	99.9	99.3	100	234	219.1	249.9	96.5	95	97.7
	D-QIV Y	Pre	22	16.8	27.9	8.6	7.4	9.9	14.7	10.4	19.9
		Post	99.1	96.9	99.9	87.5	73.8	103.7	72.2	66	77.9
B/Brisbane (Victoria)	D-QIV	Pre	78.4	75.3	81.2	30.9	28.2	33.9	48.2	44.7	51.8
		Post	100	99.5	100	244.2	227.5	262.1	97.3	96	98.3
	TIV-1	Pre	78	75	80.8	31	28.2	34	48.4	44.9	51.8
		Post	99.8	99.1	100	245.6	229.2	263.2	96.6	95.1	97.7

			Seropositivity			**GMT**			**HI Titer ≥1:40**		
Strain	**Group**	**Timing**	**%**	**LL 95% CI***	**UL 95% CI***	**Value**	**LL 95% CI***	**UL 95% CI***	**%**	**LL 95% CI***	**UL 95% CI***
	TIV-2	Pre	78.5	75.5	81.3	33.2	30.2	36.6	49.9	46.4	53.4
		Post	97.9	96.6	98.8	88.14	81.5	95.8	79.8	76.8	82.5
	D-QIV Y	Pre	30.6	24.7	37	9	7.9	10.4	12.1	8.2	17
		Post	97	93.9	98.8	86.4	72.6	102.9	71.4	65.1	77.1
B/Brisbane (Yamagata)	D-QIV	Pre	92.9	90.9	94.6	77.3	70	85.3	71.5	68.2	74.6
		Post	100	99.5	100	569.6	533.6	608.1	99.2	98.4	99.7
	TIV-1	Pre	92.1	90	93.8	77.2	70	85.2	70.2	66.9	73.3
		Post	99.9	99.3	100	224.7	207.9	242.9	94.4	92.6	95.9
	TIV-2	Pre	92.3	90.2	94	84.7	16.6	93.6	74.1	70.9	77.1
		Post	100	99.5	100	643.3	603.2	686.1	99.6	98.9	99.9
	D-QIV Y	Pre	53.4	46.8	60	13.1	11.4	15.2	20.7	15.7	26.5
		Post	100	98.4	100	167.7	144.1	195.3	90.6	86.1	94

*CI = confidence interval
Source: BLA 125127/ SN 513, CSR D-QIV 003,, Table 34, 39, page 125-129

The geometric mean titers at baseline were similar for subjects 3-17 years of age. The post-vaccination GMTs in each arm were considerably higher in all arms for these subjects. In subjects 6-35 months post vaccination GMTs were also higher post-vaccination, however GMTs and percentage of subjects with HI titers ≥ 1:40 were lower in this age cohort compared to older children.

Reviewer comment: The post-vaccination GMTs were slightly higher in the TIV-1 and TIV-2 arms than in the D-QIV arm for H1N1 influenza strain, but the post-vaccination GMTs to H3N2 and each influenza B strain were similar. Of note, GMTs post-vaccination were considerably lower after vaccination with D-QIV in children 6 to 35 months compared to vaccination with D-QIV in children 3 to 17 years of age. D-QIV will be licensed in children 3 years of age and older only. The applicant is currently studying the clinical efficacy of D-QIV in children from 6 to 35 months of age.

Reviewer's comment: For all treatment arms for subjects 3-17 years of age and for subjects 6-35 months of age who received D-QIV, the lower limit of the 95% confidence interval of the percentage of subjects with HAI titers ≥ 1:40 was greater than 70% for each influenza antigen, as recommended for demonstration of immunogenicity in the FDA Guidance for Industry.

Seroconversion rates are shown in the table below.

Table 22: D-QIV-003 – Seroconversion Rate 28 Days after Last Vaccination

Vaccine Strain	**Arm**	**% With Seroconversion**	**95%CI**	
			LL	**UL**
A/California (H1N1)	D-QIV	91.4	89.2	93.3
	TIV-1	89.9	87.6	91.8
	TIV-2	91.6	89.5	93.5
	D-QIV Y	78	72.1	83.2
A/Victoria/ (H3N2)	D-QIV	72.3	69	75.4
	TIV-1	70.7	67.4	73.8

Vaccine Strain	Arm	% With Seroconversion	95%CI	
			LL	UL
	TIV-2	71.9	68.6	75
	D-QIV Y	68.5	62.1	74.5
B/Brisbane (Victoria)	D-QIV	70	66.7	73.2
	TIV-1	68.5	65.2	71.6
	TIV-2	29.6	26.5	32.9
	D-QIV Y	68.1	61.7	74.1
B/Brisbane (Yamagata)	D-QIV	72.5	69.3	75.6
	TIV-1	37	33.7	40.5
	TIV-2	70.8	67.5	73.9
	D-QIV Y	82.3	76.8	87

Source: BLA 125127/ SN 513 CSR D-QIV 003, Table 35, page 127

Reviewer comment: The percentage of subjects with seroconversion was similar between all arms in subjects 3-17. Except for the seroconversion rate to the influenza A/H1N1 strain, the seroconversion rate was also similar for subjects 6-35 months of age who received D-QIV. All results met the criteria for demonstration of immunogenicity for accelerated approval of a TIV as outlined in the FDA Guidance (e.g. lower limit of 95% confidence interval for seroconversion rate ≥ 1:40).

Results for mean geometric increase for HI antibody are shown in the table below.

Table 23: D-QIV-003 – Mean Geometric Increase (MGI) in Antibody Titer 28 Days after Last Vaccination

Vaccine Strain	Arm	MGI	95%CI	
			LL	UL
A/California (H1N1)	D-QIV	18	16.6	19.5
	TIV-1	17.4	16	18.8
	TIV-2	19.2	17.7	20.9
A/Victoria/ (H3N2)	D-QIV	7.9	7.3	8.6
	TIV-1	7.2	6.7	7.8
	TIV-2	7.5	6.9	8.1
B/Brisbane (Victoria)	D-QIV	7.9	7.3	8.6
	TIV-1	7.9	7.2	8.6
	TIV-2	2.7	2.5	2.9
B/Brisbane (Yamagata)	D-QIV	7.4	6.8	8
	TIV-1	2.9	2.7	3.1
	TIV-2	7.6	7	8.3

Source: BLA 125127/ SN 513 CSR D-QIV 003, Table 37, page 131

Reviewer comment: There was a substantial fold increase in antibody response in all subjects post-vaccination. The fold increase in antibody titer was 7.4 or higher to all antigens in subjects 3 to 17 years of age who received D-QIV and 7.5 or higher to all antigens in subjects 6-35 months of age who received D-QIV.

The secondary endpoints also included descriptive immunogenicity by age strata (3-8 and 9-17 years). These results are shown in the tables below.

Table 24: D-QIV-003 – Seroconversion Rate 28 Days After Last Vaccination by Age

				95% CI	
Strain	**Arm**	**Age**	**% seroconversion**	**LL**	**UL**
A/California/ (H1N1)	D-QIV	3 - 8 years	91.6	88.8	93.9
		9 - 17 years	91.1	87.3	94.0
	FLUARIX	3 - 8 years	91.8	89.0	94.0
		9 - 17 years	86.7	82.4	90.3
	TIV-2	3 - 8 years	90.9	88.0	93.2
		9 - 17 years	92.9	89.4	95.6
	D-QIV-Y	6 - 17 months	61.4	49.0	72.8
		18 - 35	85.2	78.8	90.3
A/Victoria/ (H3N2)	D-QIV	3 - 8 years	75.2	71.1	79.0
		9 - 17 years	67.5	62.0	72.8
	FLUARIX	3 - 8 years	71.6	67.4	75.4
		9 - 17 years	69.2	63.7	74.3
	TIV-2	3 - 8 years	74.8	70.7	78.5
		9 - 17 years	67.0	61.3	72.3
	D-QIV-Y	6 - 17 months	52.9	40.6	64.9
		18 - 35	75.3	67.9	81.7
B/Brisbane/ (Victoria)	D-QIV	3 - 8 years	74.6	70.5	78.4
		9 - 17 years	62.6	56.9	68.1
	FLUARIX	3 - 8 years	72.0	67.8	75.8
		9 - 17 years	62.7	57.0	68.1
	TIV-2	3 - 8 years	30.6	26.6	34.8
		9 - 17 years	27.9	22.9	33.4

				95% CI	
Strain	**Arm**	**Age**	**% seroconversion**	**LL**	**UL**
	D-QIV-Y	6 - 17 months	51.4	39.2	63.6
		18 - 35	75.3	67.9	81.7
B/Brisbane/ (Yamagata)	D-QIV	3 - 8 years	77.0	73.1	80.7
		9 - 17 years	65.2	59.6	70.6
	FLUARIX	3 - 8 years	39.8	35.5	44.2
		9 - 17 years	32.5	27.3	38.0
	TIV-2	3 - 8 years	80.1	76.4	83.5
		9 - 17 years	54.9	49.0	60.6
	D-QIV-Y	6 - 17 months	74.3	62.4	84.0
		18 - 35	85.8	79.5	90.8

*CI = confidence interval
Source: BLA 125127/ SN 513, CSR D-QIV 003, Table 48, page 282

The lower limit of the 95% confidence interval was greater than the criteria for demonstration of immunogenicity (40%) recommended by the FDA Guidance for accelerated approval of TIVs for all four strains contained in the D- D-QIV vaccine and in both age groups of children 3 years and older. These criteria were also met for the antibody responses to the antigens contained in the TIV vaccines.

Reviewer comment: Seroconversion rates were similar for subjects in the 3-8 year and 9-17 year age subgroups.

Table 25 : D-QIV 003- Percentage of Subjects with Pre- and Post-Vaccination HI Antibody Titers ≥ 1:40 at Baseline and 28 Days after Last Vaccination by Age

					95% CI	
Strain	Group	Sub-group	Timing	**% with HI titer ≥ 40**	LL	UL
A/California/ (H1N1)	D-QIV	3 - 8 years	PRE	42.2	37.8	46.7
			POST	95.9	93.8	97.5
		9 - 17 years	PRE	45.4	39.7	51.2
			POST	97.7	95.3	99.1
	TIV-1	3 - 8 years	PRE	45.8	41.4	50.2
			POST	96.3	94.2	97.7
		9 - 17 years	PRE	55.2	49.5	60.8
			POST	98.1	95.8	99.3
	TIV-2	3 - 8 years	PRE	45.7	41.3	50.2
			POST	96.6	94.7	98.0
		9 - 17 years	PRE	41.4	35.8	47.2
			POST	98.0	95.7	99.3
	D-QIV-Y	6 - 17 months	PRE	8.6	3.2	17.7
			POST	63.4	51.1	74.5
		18 - 35 months	PRE	33.3	26.1	41.2
			POST	87.1	81.0	91.8
A/Victoria/ (H3N2)	D-QIV	3 - 8 years	PRE	51.8	47.3	56.4
			POST	97.5	95.8	98.7
		9 - 17 years	PRE	42.4	36.7	48.2
			POST	98.7	96.6	99.6

					95% CI	
Strain	Group	Sub-group	Timing	**% with HI titer ≥ 40**	LL	UL
	TIV-1	3 - 8 years	PRE	54.2	49.8	58.6
			POST	97.3	95.4	98.5
		9 - 17 years	PRE	43.8	38.2	49.6
			POST	98.7	96.7	99.6
	TIV-2	3 - 8 years	PRE	53.5	49.0	57.9
			POST	95.4	93.2	97.1
		9 - 17 years	PRE	47.1	41.3	53.0
			POST	98.3	96.1	99.5
	D-QIV-Y	6 - 17 months	PRE	5.7	1.6	14.0
			POST	54.9	42.7	66.8
		18 - 35 months	PRE	18.5	12.9	25.4
			POST	79.8	72.8	85.6
B/Brisbane/ (Victoria)	D-QIV	3 - 8 years	PRE	44.5	40.0	49.0
			POST	97.8	96.0	98.9
		9 - 17 years	PRE	54.3	48.5	60.0
			POST	96.7	94.0	98.4
	TIV-1	3 - 8 years	PRE	42.7	38.3	47.1
			POST	95.9	93.8	97.4
		9 - 17 years	PRE	57.8	52.1	63.4
			POST	97.7	95.4	99.1
	TIV-2	3 - 8 years	PRE	46.1	41.7	50.6
			POST	75.0	71.0	78.7
		9 - 17 years	PRE	56.2	50.4	62.0
			POST	87.9	83.6	91.4
	D-QIV-Y	6 - 17 months	PRE	1.4	0.0	7.7
			POST	53.5	41.3	65.5
		18 - 35 months	PRE	16.7	11.3	23.3
			POST	79.1	72.1	85.1
B/Brisbane/ (Yamagata)	D-QIV	3 - 8 years	PRE	64.5	60.1	68.8
			POST	99.2	97.9	99.8
		9 - 17 years	PRE	82.8	78.0	86.9
			POST	99.3	97.6	99.9
	TIV-1	3 - 8 years	PRE	60.5	56.1	64.7
			POST	91.2	88.4	93.5
		9 - 17 years	PRE	86.4	82.0	90.0
			POST	99.7	98.2	100
	TIV-2	3 - 8 years	PRE	65.4	61.1	69.6
			POST	99.8	98.9	100
		9 - 17 years	PRE	88.9	84.8	92.2
			POST	99.3	97.6	99.9
	D-QIV-Y	6 - 17 months	PRE	15.7	8.1	26.4
			POST	85.9	75.6	93.0
		18 - 35 months	PRE	22.8	16.6	30.1
			POST	92.6	87.5	96.1

*CI = confidence interval
Source: BLA 125127/ SN 513, CSR D-QIV 003, Table 49, page 283

The lower limit of the 95% confidence interval was greater than the criteria for demonstration of immunogenicity for accelerated approval of a seasonal TIV (70%) recommended in the FDA Guidance for all arms and for the respective B strains contained in each of the TIV vaccine both for subjects 3-8 years of age and 9-17 years of age.
Reviewer comment: Results for both age groups older than 3 years of age were similar.

For subjects 3-17 years of age, 37%, 37.5% and 34.9% of subjects from D-QIV, TIV-1 and TIV-2 groups, respectively, were administered a seasonal influenza vaccine in the previous three seasons. Seroconversion rates by immunization history are shown in the table below. In subjects 6-35 months, 15.5% of subjects had been administered a season influenza vaccine in the three previous seasons. Seroconversion rates by immunization history are shown in the table below.

Table 26: D-QIV-003 – Seroconversion Rates (SCR) 28 Days after Last Vaccine, by Influenza Vaccination History

		Positive History Vaccination		Negative History Vaccination	
Vaccine Strain	**Arm**	**SCR**	**LL 95%CI**	**SCR**	**LL 95%CI**
A/California (H1N1)	D-QIV	86.7	82.3	94.3	91.8
	TIV-1	85.3	81	92.8	90.1
	TIV-2	88.9	84.6	93.2	90.6
	D-QIV Y	97.2	85.5	74.5	67.8
A/Victoria/ (H3N2)	D-QIV	58	52.5	81	77.3
	TIV-1	56.6	50.9	79.7	75.9
	TIV-2	56.4	50.5	80.5	76.8
	D-QIV Y	83.3	67.2	65.8	58.7
B/Brisbane (Victoria)	D-QIV	52.7	46.8	80.6	76.8
	TIV-1	50.3	44.7	80.1	76.3
	TIV-2	18.8	14.5	35.7	31.5
	D-QIV Y	97.2	85.5	62.8	55.6
B/Brisbane (Yamagata)	D-QIV	58.7	52.9	81	77.3
	TIV-1	22.5	18	46.4	41.9
	TIV-2	55.1	49.1	79.5	75.8
	D-QIV Y	88.9	73.9	81.1	74.9

Source: BLA 125127/ SN 513, CSR D-QIV 003, Table 66, page 312

The seroconversion rates met the 40% goal for both influenza A strains for all arms both for subjects with and without prior influenza vaccination, but not for all arms for each B strains.

Reviewer comment: The percentage of subjects who seroconvert was lower in subjects who had been previously vaccinated. These results may have been related, in part, to baseline antibody titer. The baseline antibody titers were higher in subjects who had been previously immunized; therefore, although the antibody titers increased, the increases were less likely to be four-fold. When the GMTs were analyzed there was an increase in GMT for both vaccinated and unvaccinated subjects, but the increase was greater in unvaccinated subjects.

6.2.11.3 Subpopulation Analyses (003 study)

Subgroup analyses were provided by country, previous vaccination, sex, and ethnicity.

By country: The results for immunogenicity for subjects enrolled in the United States were compared to other countries (Czech Republic, France, Germany and the Philippines).

Table 27 : D-QIV 003- Data for Non-Inferiority and Superiority of D-QIV versus the Trivalent Vaccines in Terms of GMT and SCR by Country

Country	Strain	Non-Inferiority by GMT	Non-Inferiority by SCR
United States	A/California/7/2009 (H1N1)	Met criteria	Met criteria
	A/Victoria/210/2009 (H3N2)	Met criteria	Met criteria
	B/Brisbane/60/2008	Met criteria	Met criteria
	B/Brisbane/3/2007	Met criteria	Met criteria
Germany	A/California/7/2009 (H1N1)	Met criteria	Met criteria
	A/Victoria/210/2009 (H3N2)	Met criteria	Met criteria
	B/Brisbane/60/2008	Met criteria	Did not meet criteria
	B/Brisbane/3/2007	Met criteria	Did not meet criteria
France	A/California/7/2009 (H1N1)	Met criteria	Met criteria
	A/Victoria/210/2009 (H3N2)	Met criteria	Met criteria
	B/Brisbane/60/2008	Met criteria	Did not meet criteria
	B/Brisbane/3/2007	Did not meet criteria	Did not meet criteria
Czech republic	A/California/7/2009 (H1N1)	Met criteria	Met criteria
	A/Victoria/210/2009 (H3N2)	Met criteria	Did not meet criteria
	B/Brisbane/60/2008	Met criteria	Did not meet criteria
	B/Brisbane/3/2007	Met criteria	Did not meet criteria
Philippines	A/California/7/2009 (H1N1)	Met criteria	Met criteria
	A/Victoria/210/2009 (H3N2)	Met criteria	Met criteria
	B/Brisbane/60/2008	Met criteria	Met criteria
	B/Brisbane/3/2007	Met criteria	Met criteria

Source: BLA 125127/ SN 513, CSR D-QIV 003, AAR annex

Reviewer comment: For subjects in the US non-inferiority criteria were met in terms of GMT and SCR for all four strains in the Fluarix Quadrivalent vaccine. In the other sites, it is mostly by SCR that non-inferiority criteria was not met for the B lineages.

By Previous vaccination: A total of 38% of subjects in the Fluarix Quadrivalent arm had been vaccinated against influenza in the previous season. Both subjects with and without prior influenza vaccination met the criteria for the primary objective.

By sex: There was no difference for both males and females and they both met primary end-point.

By race/ethnicity: Both Caucasians and non-White Caucasians met criteria for non-inferiority.

Reviewer comment: Subgroup analyses were performed by country, by history of influenza vaccination in previous three years, by gender, and by race/ethnicity. No substantial differences were observed between any subgroups.

6.2.12 Safety Analyses

6.2.12.1 Methods

The analysis of safety was performed on the Total Vaccinated Cohort, which included x subjects 3 to 17 years of age: 915 subjects of whom received D-QIV, 912 subjects Fluarix (TIV-1), and 911 subjects TIV-2. The safety cohort also included 277 subjects 6-35 months who received D-QIV (DIV-Y arm). Please see section 6.2.7.

6.2.12.2 Overview of Adverse Events

Information on solicited adverse events, general and local and unsolicited was collected on the Day of vaccination and during the six subsequent Days. The incidence is shown in the table below.

Table 28: D-QIV-003 – Percentage of Subjects with Any Solicited Adverse Reaction

Type of Solicited Adverse Reaction	D-QIV	TIV-1	TIV-2	D-QIV Y
Any Solicited Adverse Reaction	66%	63%	64%	78%
Any Grade 3 Solicited Adverse Reaction	7%	7%	5%	13%
General Solicited Adverse Reaction	44%	44%	43%	64%
Grade 3 General Solicited Adverse Reaction	4%	4%	3%	11%
Any Local Solicited Adverse Reaction	54%	52%	52%	54%
Grade 3 Local Solicited Adverse Reaction	4%	4%	2%	2%

Source: BLA 125127/ SN 513, CSR D-QIV 003, Tables 40-41, pages 140

The percentages of subjects with solicited adverse events and Grade 3 solicited adverse events were similar between the three study arms for children ages 3-18. Subjects 6-35 months had more solicited adverse reactions than the older aged children, which was largely due to the increase in general solicited adverse reactions in the younger children.

The types of individual solicited local adverse events are shown in the table below.

Table 29: D-QIV-003 – Percentage of Subjects with Individual Solicited Local Adverse Events (AEs)

Type of Local Solicited AE	D-QIV	TIV-1	TIV-2	D-QIV Y
Pain	49%	47%	46%	42%
Grade 3 Pain	2%	2%	1%	2%
Redness	25%	24%	23%	36%
Grade 3 Redness (≥50 mm)	1%	0.3%	0.7%	0.4%
Swelling	22%	21%	18%	24%
Grade 3 Swelling (≥50 mm)	1%	1%	0.3%	0%

Source: BLA 125127/ SN 513, CSR D-QIV 003, Table 42, page 145

Pain was the most commonly reported of the local solicited adverse reactions. Grade 3 pain was rarely reported. Redness was more commonly reported in the younger subjects, and 1% or less of subjects had Grade 3 redness at the injection site. Swelling at the injection site was reported similarly in all three arms and grade 3 swelling was reported in 1% or less in all arms.

Reviewer comment: The results between arms were similar and severe solicited local adverse reactions were uncommon.

The percentage of subjects reporting individual local solicited adverse reactions by age cohort and by vaccine dose is shown in the following table.

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Table 30: D-QIV-003 – Percentage of Subjects with Individual Solicited Local Adverse Events in Subjects by Age and Vaccination Dose.

	3-8 Years									9-17 years		
	Overall			1st Vaccination			2nd Vaccination					
Type of Local Solicited AE	**D-QIV**	**TIV-1**	**TIV-2**	**D-QIV**	**TIV-1**	**TIV-2**	**D-QIV**	**TIV-1**	**TIV-2**	**D-QIV**	**TIV-1**	**TIV-2**
Pain	48%	46%	46%	39%	38%	37%	36%	32%	32%	52%	50%	46%
Grade 3 Pain	2%	2%	2%	1%	2%	0.5%	1%	1%	1%	2%	2%	1%
Redness	25%	25%	23%	22%	21%	20%	15%	16%	16%	25%	21%	22%
Grade 3 Redness (≥50 mm)	2%	0.5%	0.2%	2%	0.3%	0.2%	0.2%	0%	0%	0%	0%	2%
Swelling	23%	22%	19%	19%	16%	14%	14%	13%	12%	19%	20%	16%
Grade 3 Swelling (≥50 mm)	2%	0.5%	0.2%	1%	0.1%	0%	1%	0%	0.2%	0.3%	2%	0.6%

Source: BLA 125127/ SN 513, CSR D-QIV 003, Supplement 390, page 592

Pain was reported more frequently in subjects 9-17 years of age had more pain than in subjects 3-8 years of age. The incidence of individual local solicited adverse events was otherwise similar in subjects 3-8 years of age and 9-17 years of age. In general, more local solicited adverse reactions were reported after the first vaccination than the second vaccination in unprimed subjects.

Reviewer comment: The percentage of subjects with individual local solicited adverse reactions was similar in the two age groups except for pain, which was reported more commonly in the older cohort. This may have been related to the inability to adequately express pain at the injection site in the youngest children.

The incidence of individual solicited general adverse events is shown in the table below. Different types of individual solicited general adverse reactions were followed in children younger than six years of age and in those six years of age and older.

Table 31: D-QIV-003 – Percentage of Subjects with Individual Solicited General Adverse Reactions in Subjects Younger than 6 Years of Age

	D-QIV	TIV-1	TIV-2	D-QIV Y
Drowsiness	23%	18%	21%	30%
Grade 3 Drowsiness	2%	1%	0.7%	2%
Irritability	22%	18%	19%	43%
Grade 3 Irritability	1%	0.6%	1%	4%
Loss of appetite	20%	13%	17%	30%
Grade 3 loss of appetite	1%	1%	1%	4%
Fever	17%	16%	15%	29%

	D-QIV	TIV-1	TIV-2	D-QIV Y
Grade 3 Fever n(≥39ºC)	1%	0.6%	1%	7%

Source: BLA 125127/ SN 513, CSR D-QIV 003, Table 43, page 148-150

Table 32: D-QIV 003 – Percentage of Subjects with Individual Solicited General Adverse Reactions in Subjects 6 Years of Age and Older

	D-QIV	TIV-1	TIV-2
Fatigue	21%	20%	18%
Grade 3 Fatigue	2%	1%	0.6%
Gastrointestinal	11%	11%	8%
Grade 3 Gastrointestinal	1%	1%	0.3%
Headache	18%	21%	18%
Grade 3 Headache	1%	0.7%	0.8%
Joint Pain at Other Location	11%	11%	8%
Grade 3 joint pain	0.3%	0.7%	0.3%
Muscle aches	19%	18%	17%
Grade 3 Muscle Aches	0.7%	2%	0.5%
Shivering	7%	5%	6%
Grade 3 Shivering	0.5%	0.5%	0.2%
Fever	8%	10%	8%
Grade 3 Fever	1%	0.8%	0.5%

Source: BLA 125127/ SN 513, CSR D-QIV 003, Table 44, page 155-159

The incidence of each individual general solicited adverse reactions was similar between subjects in the D-QIV, TIV-1, and TIV-2 arms, except for loss of appetite, which was reported in a statistically significantly higher percentage of subjects in the D-QIV and TIV-2 arms compared to the TIV-1 arm.

Reviewer comment: Overall, the percentage of subjects with individual solicited general adverse reactions was no higher in the D-QIV arms than the TIV arms.

When the percentage of unprimed subjects with individual general adverse reactions by dose were analyzed, there were fewer individual adverse reactions reported after the second dose than after the first.

Information on unsolicited adverse events was collected for the 28 Days post-vaccination. Unsolicited adverse events were reported in a total of 31% of subjects from the D-QIV group, 33.4% in the TIV-1 group and 33.8% in the TIV-2 group. Of these 2.2% in the D-QIV group, 4.1% in the TIV-1 and 2.9% in the TIV-2 group were Grade 3 adverse events. Medically attended visits were reported in 29.6% in the D-QIV group, 30.5% in TIV-1 group and 33.3% in TIV-2 group. Nasopharyngitis was the most frequently reported unsolicited adverse event with a medically attended visit in all three groups (4.3%, 4.7% and 6.1% respectively for D-QIV, TIV-1 and TIV-2).

Unsolicited AEs by age group is shown in the following table.

Table 33: D-QIV-003 – Percentage of Subjects with >1% Unsolicited AEs by Age

	6-35 mos	3-8 years			9-17 years		
Type of Unsolicited AE	**D-QIV**	**D-**	**TIV-1**	**TIV-2**	**D-**	**TIV-1**	**TIV-2**

	6-35 mos	3-8 years			9-17 years		
	Y	QIV			QIV		
Nasopharyngitis	13.4%	7.2%	8.2%	9.2%	1.9%	3.5%	2.9%
Upper Respiratory Infection	9.4%	6.9%	7.4%	5.7%	2.2%	2.2%	3.8%
Cough	7.6%	6%	5.5%	6.2%	1.3%	0.9%	2.6%
Pyrexia	6.5%	3.5%	3.2%	4.4%	0.6%	1.3%	0.6%
Rhinitis	4%	2%	2.2%	2%	0.9%	0.3%	0.6%
Vomiting	1.4%	2.3%	2.2%	1.8%	0.6%	0.9%	0.3%
Bronchitis	10.5%	2%	0.7%	2%	0.3%	0.3%	0%
Abdominal pain	0%	0%	1.2%	1%	0%	0.3%	0.3%
Pharyngitis	2.2%	1%	1.5%	1%	0%	1.3%	1%
Headache	0.4%	1.2%	1%	1.5%	1.6%	1.3%	1.6%
Oropharyngeal pain	0%	1%	1%	1.3%	1.6%	1.6%	1.6%

Source: BLA 125127/ SN 513, CSR D-QIV 003, Supplement 421, page 757

Nasopharyngitis, upper respiratory infection and cough were the most common unsolicited AEs.

Reviewer comment: The incidence of unsolicited AEs was similar in the three vaccine arms. The types of unsolicited AEs were consistent with illnesses commonly reported in children. Finally, there was a low incidence of Grade 3 AEs in all vaccine arms.

6.2.12.3 Deaths

There was one death in the study. The subject was 3 years old who died due in a road traffic accident 4 months after receiving TIV-1.

6.2.12.4 Nonfatal Serious Adverse Events

Serious adverse events were reported in 21 subjects: 8 (0.9%) in the D-QIV arm, 6 (0.7%) in the TIV-1 arm and 7 (0.8%) in the TIV-2 arm. There were a total of 27 serious AEs in these subjects.

Table 34: D-QIV-003 - Number of Serious Adverse Events Reported for the Entire Study Period Post-Vaccination by Age Group

	3-8 years			9-17 years		
Type of Solicited AE	**D-QIV**	**TIV-1**	**TIV-2**	**D-QIV**	**TIV-1**	**TIV-2**
1st degree AV block	1					
Lymphadenitis	1					
Gastroenteritis	1					
Myocarditis	1	0	0	0	0	0
Concussion	2	0	2	2	0	0
Enteritis	1	0	0	0	0	0
Infectious Monomucleosis	1	0	0	0	0	0
Tonsillitis	1	0	0	0	0	0
Exanthem	1	0	0	0	0	0
Pneumonia	0	2	0	0	0	0
Dengue Fever	0	2	0	0	0	0

	3-8 years			**9-17 years**		
Exanthem	0	0	1	0	0	0
Rotavirus	0	0	1	0	0	0
Suicidal ideation	0	0	1	1	0	0
Appendicitis	0	0	1	0	0	0
Peritonsillar abscess	0	0	0	1	0	0
Abdominal Trauma	0	0	0	0	1	0
Diabetes Ketoacidosis	0	0	0	0	0	1

Source: BLA 125127/ SN 513, CSR D-QIV 003Table 52, page 184

Reviewer comment: None of the serious adverse events were judged to be vaccine-related. All but two SAEs resolved (suicidal ideation/psychiatric disorder and Diabetic Ketoacidosis which led to a diagnosis of Type 1 Diabetes Mellitus persisted). The duration of the SAEs was from 1 to 37 Days. There was no increase in incidence of any individual SAE or in SAEs in any organ system noted. There were no differences noted by treatment arm.

6.2.12.5 Adverse Events of Special Interest (AESI)

There were two potential immune-mediated diseases. A 14 year old female subject developed Bell's palsy 91 Days after receiving TIV-1. This resolved 3 weeks after onset. Another subject, an 11 year old female developed Type 1 Diabetes Mellitus.

Reviewer's comment: None of the potential immune-mediated diseases appear to be vaccine related.

6.2.12.6 Clinical Test Results

There were no clinical laboratory tests included in this study.

6.2.12.7 Dropouts and/or Discontinuations

Three subjects discontinued the study due to adverse events. Two subjects were from the D-QIV vaccine arm: a 5 year old discontinued after experiencing bacterial enteritis 14 Days after receiving the vaccine and a 3 year old died secondary to a road traffic accident. One subject from the TIV-1 arm discontinued the study secondary to viral pneumonia 30 Days after receiving the vaccine.

Reviewer's comment: In the opinion of this reviewer, none of the discontinuations appear to be vaccine related.

6.2.13 Comments and Conclusions

The results of Study D-QIV 003 provide the primary basis for demonstration of immunogenicity and safety of Fluarix Quadrivalent in subjects 3-17 years. In this study, the primary objective of immunologic non-inferiority and the secondary objective of superiority were met.

The most common adverse events associated with D-QIV in this study were pain at the injection site for all subjects and drowsiness, irritability and loss of appetite for children 3 to less than 6 years of age and fatigue, muscle aches and headaches for children 6 to less than 18 years of age. There was no increase in the incidence of unsolicited individual AEs or AEs with a specific organ system. Finally, serious adverse events were uncommon. In summary, there were no safety

signals identified in the review of this study, and the safety results for subjects in the D-QIV arm were similar to those observed for subjects in the TIV arms.

6.3 Phase I and II studies

The results of two non-IND Phase I and/or Phase II studies were submitted to support the safety and immunogenicity of Fluarix Quadrivalent.

6.3.1 Study D-QIV 001

A Phase I/II randomized, single-blind, controlled study in adults aged 18-60 years of age to evaluate the immunogenicity, safety and reactogenicity of Fluarix Quadrivalent.

Study D-QIV 001 was an immunogenicity and safety study comparing Fluarix Quadrivalent, Fluarix, ----------(b)(4)----------. Subjects were randomized in a 1:1:1:1 ratio to receive either D-QIV, ---------(b)(4)--------- or TIV.

----------*(b)(4)*----------.

Subjects received a single 0.5 mL intramuscular dose of study vaccine on Day 1 and were returned to the study clinic on Days 21 and 180. Information on solicited adverse reactions was collected for seven Days post-vaccination, information on unsolicited adverse events was collected for 21 Days post-vaccination, and information on serious AEs was collected for 180 Days post-vaccination. Blood samples were obtained on Days 1 and 22 for antibody response. Antibody response was analyzed by calculations of GMTs, seroconversion rate, and percentage of subjects with post vaccination HI titers of 1:40 or higher.

A total of 420 subjects were enrolled: 105 subjects were enrolled in each vaccine arm. The mean age of subjects was 37.5 years old. 60% of subjects were female and all subjects (except one) were of White-Caucasian heritage.
The primary objectives on immunogenicity were met. QIV was non inferior compared to TIV in terms of GMT ratios for the strains contained in the TIV and superior to the TIV for the B strain no included in the trivalent vaccine. ----------(b)(4)----------.

The safety results for solicited adverse reactions were similar in the two -----(b)(4)----- arms and were similar to those observed in other studies of Fluarix Quadrivalent and described previously in this review. Unsolicited adverse events were consistent with illnesses frequently seen in adults.

Reviewer comment: The most common adverse events associated with Fluarix Quadrivalent in this study were reactogenicity events, particularly pain at the injection site, fatigue, and headache. The majority of these reactogenicity AEs were mild or moderate in intensity. There was no increase in the incidence of unsolicited individual AEs or AEs with a specific organ system. Finally, serious adverse events were uncommon. In summary, there were no new safety signals identified in the review of this study.

D-QIV 002

A Phase II, double-blinded, multicenter, randomized study in children 18-47 months of age to evaluate the immunologic non-inferiority to the three influenza strains in Fluarix Quadrivalent that were also contained in Fluarix. Approximately, one-third (N=192) of subjects were a subgroup of children who had participated in a previous immunogenicity and safety study of Fluarix in children (study 111751); two-thirds of subjects enrolled (N=407) were newly enrolled, unprimed children.

Study subjects were randomized in a 1:2:1:2 fashion to a primed TIV group, unprimed TIV group, primed D-QIV and unprimed D-QIV group. Unprimed subjects received two doses of vaccine 28 Days apart. Immunogenicity assessments were performed on serum samples collected pre- and post-vaccination. Post-vaccination serum samples were collected 28 days after vaccination in primed subjects, 28 days after the first vaccination in one-half of unprimed subjects, and 28 days after the second vaccination in the other one-half of unprimed subjects. The primary endpoint was to evaluate inferiority of the influenza strains in Fluarix Quadrivalent compared to Fluarix by geometric mean titers only. Seroconversion rate was not assessed as a primary endpoint. In addition, non-inferiority of the second influenza B strain in the quadrivalent vaccine could not be assessed, since a study group who received a second trivalent formulation was not included for immunogenicity comparisons.

The study was conducted in Mexico. Overall 599 subjects were enrolled, 298 were vaccinated with D-QIV and 301 with TIV. The mean age was 30 months. 47.6% of subjects were female. All subjects were of American Hispanic or Latino ethnicity.

As observed in the other Fluarix Quadrivalent studies, D-QIV was non-inferior in terms of GMTs compared to Fluarix for the three strains included in the trivalent vaccine. In addition Fluarix Quadrivalent was superior in terms of GMTs to the Fluarix for the B strain not included in the trivalent vaccine. Higher GMTs were observed in primed versus unprimed subjects.

Similarly to study D-QIV 003, injection site pain, loss of appetite and irritability were the most frequently reported adverse reactions. Nasopharyngitis was the most common reported unsolicited AE. Two serious AEs occurred; both were in the TIV group: one subject developed bronchopneumonia at Day 87 and one subject developed urticaria at Day 107.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

There is only one indication which is for active immunization for the prevention of disease cause by 2 influenza A subtype viruses and 2 B lineage viruses.

7.1.1 Methods of Integration

The results of the two Phase III studies were included in this application. Study D-QIV 008, in 3036 adults subjects receiving D-QIV 008 and D-QIV 003 in 915 pediatric subjects age 3-17 years receiving D-QIV provided support for immunogenicity and safety respectively in adult and pediatric population.

Although the immunogenicity endpoints of both studies were antibody response to vaccination, the results of the two studies can not be pooled due to the different populations studied and assays being performed in different laboratories. Please see Section 6.0 for discussions of the results of both studies.

7.1.8 Persistence of Efficacy

Vaccination against seasonal influenza is recommended yearly because of frequent changes in circulating strains. See "Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2011," MMWR 2011 August 26; 60 (33):1128-1132.

7.1.9 Product-Product Interactions

In the studies of Fluarix Quadrivalent included in this application, Fluarix Quadrivalent was administered alone with concomitant administration of other vaccines forbidden by the study protocols. The proposed package insert states that "There are insufficient data to assess the concurrent administration of Fluarix Quadrivalent with other vaccines."

7.1.11 Efficacy Conclusions

The effectiveness of Fluarix Quadrivalent is supported by the results from studies Flu D-QIV-008 and Flu D-QIV-003.

Vaccine effectiveness of Fluarix Quadrivalent was demonstrated in a large placebo controlled trial of subjects from 18 years of age and older (Flu D-QIV-008), including in the subgroup of subjects 65 years of age and older, and in a large trial in pediatric subjects from 3-17 years of age (Flu D-QIV-003). The antibody response to the influenza antigens contained in Fluarix Quadrivalent was non-inferior to the antibody response to the corresponding antigens in the trivalent formulation. In addition, the antibody response to the influenza B antigen in the D-QIV was superior to the cross reactive antibody response to the influenza B antigen from a different lineage, therefore, inclusion of a second influenza B strain in the seasonal influenza vaccine provided an immunologic benefit compared to use of a trivalent formulation.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The safety database included 4, 354 subjects who received at least on dose of Fluarix Quadrivalent. All subjects were followed for local and systemic reactogenicity for seven Days post-vaccination. All unsolicited adverse events were followed for 21 Days in the majority of subjects. Although the follow up for serious adverse events and for adverse events leading to premature study discontinuation was only 21 Days in the TIV-2 arm of the adult Phase III study, follow up was 180 Days in all the other arms of both Phase I/II and III studies. In the opinion of this reviewer, the size of the safety database and amount of follow-up was sufficient to assess the safety of a unadjuvanted, quadrivalent influenza vaccine.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The studies used in this reviewer's integrated summary of safety were D-QIV 001, D-QIV 002, D-QIV 008 and D-QIV 003.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

In the four studies, a total of 4,354 subjects were exposed to at least one 0.5 mL intramuscular dose of Fluarix Quadrivalent. This is the dose and the method of administration that will be described in the package insert. Of these subjects, 1517 were over the age of 65, and % were younger than 18 years. The percentage of females in the studies ranged from 48% to 60% in the four studies. The majority of subjects studied were Caucasian: 57% to 100% in 001; in one study (Flu D-QIV 002) all subjects were of Hispanic or latino ethnicity. The population illustrated in these studies should reflect the that of the U.S. population.

8.2.3 Categorization of Adverse Events

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

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

The identical solicited adverse reactions were followed in adults in the Phase III and Phase II studies. Similarly the identical solicited AEs were followed in the pediatric population in the Phase III and Phase II studies. Information on solicited adverse reactions was collected for seven Days (Day of vaccination and subsequent six Days) in all four studies. Information on unsolicited adverse events was collected for 21 Days post-vaccination in adult studies and 28 Days post vaccination in the pediatric studies. Information on serious adverse events, deaths, and adverse events leading to premature study discontinuation were collected for the entire study period, which was 180 Days post-vaccination in all four studies except for the TIV-2 arm of the adult Phase III study.

The collection of safety results was almost identical in each study, however, results can not be pooled because of the differences by age.

8.4 Safety Results

8.4.1 Deaths

There were 9 deaths in subjects who received Fluarix Quadrivalent in the four studies included in this summary. In the same studies, there were four deaths in the TIV-1 arm and no deaths in the TIV-2 arm. Case narratives of all adult deaths are described in section 6.1.12.3.

None of the deaths were judged as vaccine-related. Only two deaths were reported within 30 Days of vaccination; one was an 84 year old female with extensive cardiovascular disease who developed erysipelas two Days after receiving the vaccine and died suddenly, the other subject was 69 years old with a history of ischemic heart disease who died two weeks later of cardiac disorder, necropsy report is pending. There was only one death in a pediatric subject: a 3 year old who died secondary to a motor vehicle accident.

There were more deaths in the D-QIV arm, however they were all from the D-QIV-008 study, where subjects were randomized in a 3:1:1 ratio to D-QIV, TIV-1 or TIV-2 and in which 3036 subjects received D-QIV and only 1010 received TIV-1 and 610 received TIV-2. Therefore, there was no difference in the percentage of subjects dying in the three arms. In addition, all the deaths in D-QIV arm were subjects 71 years of age and older. There was no increase in deaths due to adverse events in a single system organ class and no increase in any individual adverse event leading to deaths. The majority of deaths occurred more than one month after vaccination with Fluarix Quadrivalent. In the opinion of this reviewer, none of the deaths were related to study vaccination.

8.4.2 Nonfatal Serious Adverse Events

In the age 3 to 17 year cohort, the percentage of subjects with SAEs was ≤ 1% in each arm (14 in Fluarix Quadrivalent recipients, 7 in the TIV-1 recipients, and 7 in the TIV-2 recipients. There were no individual SAEs reported in more than two subjects in any arms. Four SAEs were reported within 30 Days of study vaccination and included: bacterial gastroenteritis, Dengue and pneumonia (in same subject) and a concussion.

In the age 18-64 year cohort there were 18 SAEs reported in subjects who received Fluarix Quadrivalent and 6 who received TIV-1. The percentage of subjects in this cohort with SAEs was ≤ 1% in each arm. There were no individual SAEs reported in more than two subjects in any arms. Five SAEs were reported within 30 Days, 3 in the D-QIV arm which were: asthma exacerbation, pneumonia and non-cardiac chest pain and 2 in the TIV-1 arm which were foot fracture and nephrolithiasis.

In the elderly cohort (65 years and older), there were 70 SAEs reported in subjects who received Fluarix Quadrivalent and 18 in the TIV-1 arm and one in the TIV-2 arm. The percentage of subjects in this cohort with SAEs was ≤ 1% in each arm. The majority of

serious adverse events were reported in cardiovascular system and were common diseases reported in the elderly such as myocardial infarction, congestive heart failure and stroke. SAEs reported more than twice in the D-QIV arm included pneumonia, gastric adenoma and cardiac failure. There was no single preferred term that was reported at an increased rate in the cardiovascular class or other organ classes. Seventeen SAEs in elderly subjects were reported within 30 Days of vaccination in the Fluarix Quadrivalent arm: gastric ulcer hemorrhage, urinary tract infection, liver carcinoma, cardiac failure and ischemia, rectal carcinoma, pyelonephritis, bronchospasm, leg weakness and pneumonia. Four SAEs were reported within 30 Days in the TIV-1 arm which were: stroke, peripheral vertigo, pneumonia and upper gastrointestinal hemorrhage. There was one SAE reported within 30 Days in the TIV-2 arm which was worsening artherosclerosis.

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

8.4.3 Study Dropouts/Discontinuations

Sixteen subjects withdrew from a study prematurely due to adverse events. This includes the 13 deaths described in Section 8.4.1 and 3 additional subjects. Two subjects who received Fluarix Quadrivalent discontinued a study prematurely:

- Subject 861 was a 70 year old female and developed rectal carcinoma on Day 22.
- Subject 915 was a 5 year old male and developed gastroenteritis on Day 14.

None of these adverse events are considered vaccine related.

8.4.4 Common Adverse Events

Solicited adverse reactions that were observed in more than 10% of pediatric subjects who received Fluarix Quadrivalent were injection site pain, erythema and swelling; drowsiness, irritability; loss of appetite; fatigue; muscle aches; headache; arthralgia and gastrointestinal symptoms. Solicited adverse reactions reported in more than 10% of adult and elderly subjects were pain, muscle aches, headache and fatigue.

In the 3-17 year cohort, the percent of subjects who reported an unsolicited adverse event in the 28 Days post-vaccination ranged from 31-38.9% in the Fluarix Quadrivalent arms, from 38.4-39.2% in the TIV-1 arms and 33.8% in the TIV-2 arm. In the Fluarix Quadrivalent arms, nasopharyngitis was reported in 7-8% of subjects (7-8% in TIV-1 arm and 9% in TIV-2 arm), upper respiratory infection in 5-7% of subjects (7% in TIV-1 arm and 6% in TIV-2 arm) and cough in 5-6% of subjects (5% in TIV-1 arm and 4% I TIV-2 arm).

The percentage of adult subjects from 18-64 years of age who reported an unsolicited adverse event 21 Days post vaccination ranged from less than 1% to 6% in D-QIV arms and less than 1% to 10.5% in TIV-1 arms. The most commonly reported unsolicited AEs were common illnesses reported in adults such as pharyngitis, cough and headache. In the analysis of both adult studies combined, no single unsolicited AEs was reported in more than 1% of subjects in Fluarix Quadrivalent arm.

The percentage of elderly subjects (65 years and older) reporting unsolicited AEs in the 21 Days post vaccination was less than 1 % in all three vaccine arms.

8.4.5 Clinical Test Results

There were no clinical safety laboratory tests performed in any of the studies submitted to this supplemental BLA.

8.4.6 Systemic Adverse Events and 8.4.7 Local Reactogenicity

Approximately half of all pediatric subjects aged 3-17 years of age who received Fluarix Quadrivalent reported a solicited adverse reaction in the seven Days post-vaccination and there was no additional reactogenicity secondary to the second B strain as this was similar to subjects in TIV-1 and TIV-2 arms. The most frequently reported local solicited adverse reactions were pain (49%), redness (25%) and swelling (22%); the most frequently reported systemic solicited adverse reactions in children 3 to less than 6 years were drowsiness (23%), irritability (22%) and loss of appetite (20%) and in children 6 to less than 18 years of age were fatigue (21%), muscle aches (19%) headache (18%), arthralgia (115) and gastrointestinal symptoms (11%).

Adult subjects reporting a solicited adverse reaction in the seven Days post vaccination in the Fluarix Quadrivalent arm ranged from 37-73% in the two adult studies. The most frequently reported local solicited adverse reactions were injection site pain in 52.5% of subjects; the most frequently reported systemic solicited adverse reactions were muscle ache, headaches and fatigue which were all reported in 22% of adult subjects.

Fifteen percent of elderly subjects who received Fluarix Quadrivalent reported a solicited adverse reaction. This included 20% with pain at injection site. The most frequently reported systemic solicited adverse reactions were muscle aches, headaches and fatigue which were all reported in 10% of elderly subjects.

8.4.8 Adverse Events of Special Interest

There was a single subject with a hypersensitivity reaction after vaccination with Fluarix Quadrivalent. The subject developed pruritus 38 Days after receiving the vaccine, required treatment with a steroid injection, and was hospitalized for one Day. This resolved without sequelae. No AES of hypersensitivity reaction or allergic reaction to the comparator vaccines were reported. There was no increase in the percentages of subjects with urticaria in subjects who received Fluarix Quadrivalent. Because the hypersensitivity reaction was not temporary related to vaccination, it is unlikely to be due to the study vaccine. In the opinion of this reviewer, there does not appear to be an increased risk of serious allergic reactions following vaccination with Fluarix Quadrivalent.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

The same dose of Fluarix Quadrivalent was studied in adults and in children in the studies included in this supplemental BLA; therefore, there are no safety data to compare different antigen doses of the vaccine formulation. Of interest, the quadrivalent formulation did have a higher antigen content that the control vaccine, however, safety results were similar for the quadrivalent and trivalent formulations. In addition, unprimed pediatric subjects 3 to 8 years of age received two study vaccinations administered 28 Days apart. More local and systemic solicited adverse reactions were reported after the first vaccine compared to the second vaccine. This is shown in the table below:

Table 35: Percentage of Subjects with Solicited AEs after First and Second Vaccination with Fluarix Quadrivalent

	Subjects 3-8 years	
	1st vaccination	2nd vaccination
Local solicited AEs		
Pain	39%	36%
Redness	22%	15%
Swelling	19%	14%
Systemic solicited AEs		
Drowsiness	17%	12%
Irritability	17%	15%
Fatigue	17%	13%
Muscle aches	17%	10%
Loss of appetite	16%	9%
Gastrointestinal	10%	4%
Joint pain	9%	7%

8.5.2 Time Dependency for Adverse Events

The majority of adverse events post-vaccination were capture in the week post-vaccination as solicited adverse reactions. The majority of these AEs were mild and resolved by Day 7. No other adverse events had a temporal relationship to study vaccination.

8.5.3 Product-Demographic Interactions

Safety results were analyzed by age, gender and ethnicity in the two Phase III studies. The safety profile differed by age with fewer adverse events reported in elderly subjects and a higher number reported in the pediatric population. The overall incidence of all adverse events in subjects 3-17 years of age was reported in 66% of subjects, in adults 18-64 years of age 64%, and 35% in subjects 65 years of age and older. The percentage of subjects with individual local solicited adverse reactions was higher in the pediatric population age 3-17 years old and lowest in the elderly population with the exception of

pain which was reported in 51% of adult subjects 18-64 years of age and 49% of subjects 3-17 years. The difference in pain may have been related to the inability of younger children to verbally express pain. Individual systemic solicited adverse reactions were reported in either the same or higher percentage of pediatric as adult subjects except for headaches (reported in 18% of pediatric and in 22% of adult subjects), and muscle aches (reported in 19% in pediatric and in 23% of adult subjects). Individual systemic solicited adverse reactions, except shivering, were reported in fewer elderly subjects compared to adult and pediatric subjects. The lower rate of solicited adverse reactions in elderly subjects was likely due to immunosenescence.

In the analysis of safety by gender, the percentage of adult subjects with any solicited adverse reaction was higher in females (55%) than in males (41%). There was an increase in the percentage of female subjects with each individual local and systemic solicited adverse reaction compared to males. The rate of subjects with severe adverse reactions was low and similar in females and males. A higher percentage of females with solicited adverse reactions were also reported in pediatric subjects. The reason for this difference is unclear.

The majority of adult subjects (68%) who received Fluarix Quadrivalent in the Phase III study were Caucasian. The percentage of subjects with local solicited adverse reactions was similar in Caucasians compared to non-Caucasians. The percentage of individuals with systemic solicited adverse reaction was greater than 5% only for fatigue (14% Caucasian and 20% of non-Caucasians). In the Phase III pediatric study there was an equal number of Caucasian (54%) and non-Caucasian subjects (46%).

8.5.4 Product-Disease Interactions

N/A

8.5.5 Product-Product Interactions

N/A

8.5.6 Human Carcinogenicity

N/A

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

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

8.5.8 Immunogenicity (Safety)

No safety concerns correlate with antibody response.

8.5.9 Person-to-Person Transmission, Shedding
Fluarix Quadrivalent is an inactivated influenza vaccine; therefore, there is no shedding of influenza virus post-vaccination.

8.6 Safety Conclusions

Injection site pain was reported in more than 10% of adult subjects, and injection site pain, redness and swelling were reported in more than 10% of subjects 3-17 years of age. Headache, fatigue and myalgia in the week after vaccination were also common and reported in more than 10% of adult subjects who received Fluarix Quadrivalent. Drowsiness, irritability and loss of appetite were the most common solicited general adverse events seen in children 3 to less than 6 years of age. Fatigue, muscle aches, headache, arthralgias and gastrointestinal symptoms were the most common solicited general adverse events seen in more than 10% of subjects 6 to less than 18years of age.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

The applicant has conducted preclinical reproductive and developmental toxicity study on Fluarix Quadrivalent (Please see the toxicology review of the application). No clinical trial have been conducted in pregnant women, therefore, Fluarix Quadrivalent will be labeled as pregnancy category B.

A total of 6 women became pregnancy during safety follow-up of the studies in this application. This included 3 in the Fluarix Quadrivalent arms that resulted in one healthy newborn without congenital anomalies and 2 unknown outcomes and 3 in the TIV-1 arm that resulted in 2 unknown outcomes and 1 elective abortion.
None of the studies were designed to study Fluarix Quadrivalent during pregnancy and all study protocols excluded enrollment of pregnant women. However, no safety signals have been apparent in the Fluarix trivalent pregnancy registry, multiple studies of inactivated flu vaccines in pregnancy have not suggested a safety signal, and the reproductive toxicology studies on Fluarix quadrivalent support the safety in pregnancy. Taken together, these data support the proposed pregnancy category B.

9.1.2 Use During Lactation

The vaccine has not been evaluated in nursing mothers and it is not known if Fluarix Quadrivalent is excreted in human milk.

9.1.3 Pediatric Use and PREA Considerations

For children age 3 years and older, PREA requirements were fulfilled by safety and immunogenicity data from study D-QIV-003 and D-QIV-002. Study D-QIV-003 was a Phase III safety and immunogenicity study in children age 3-17 years. Study D-QIV-002 was a Phase II safety and immunogenicity study in children age 18-47 months.

The applicant initiated, as part their clinical development plan, an evaluation of Fluarix Quadrivalent in children 6 months through 35 months of age (study D-QIV-004). The trial is ongoing and clinical endpoint efficacy data are expected to be available in 2013.

The PREA requirement for this age group was deferred, since waiting for the data from D-QIV-004 would delay the availability of D-QIV for individuals ≥3 years of age.

The PREA requirement for studies in children ages 0 to <6 months were waived, because available data in infants <6 months of age indicate that serum antibody responses to inactivated influenza vaccines in this age group are not as robust as in older children due to inherent immaturity of the immune system and interference from maternal antibody. Thus, use of Fluarix Quadrivalent in infants <6 months of age would provide no meaningful therapeutic benefit over initiating vaccination at 6 months of age, and this vaccine is not likely to be used in a substantial number of infants < 6 months of age.

The requirement for studies in ages 6 months to < 3 years of age were deferred; because the product is ready for approval in patients 3 years of age and older, and pediatric studies in younger subjects have not been completed.

9.1.4 Immunocompromised Patients

Fluarix Quadrivalent has not been studied in immmunocompromised patients.

9.1.5 Geriatric Use

Elderly subjects were enrolled in Study D-QIV 008. In this study, subjects were stratified by age: 18-64 years and 65 years and older; in addition, the study examined results for subjects 18-74 years of age and 75 years and older. The immunogenicity results from subjects 65 years and older are shown in the following table.

Table 36: Point Estimate (Lower Bound 95% Confidence Interval) for Immunogenicity Results in Subjects 65 Years of Age and Older

		Seroconversion		% ≥ 1:40 Day 22	
Strain	Group	%	LL 95% CI*	%	LL 95% CI*
A/California/7/2009 (H1N1)	D-QIV	72	69	88	85
	TIV-1	75	69	88	85
	TIV-2	79	73	90	86
A/Victoria/210/2009 (H3N2)	D-QIV	77	74	96	94
	TIV-1	61	55	96	93
	TIV-2	66	60	98	95
B/Brisbane/60/2008	D-QIV	48	45	99	98
	TIV-1	45	39	98	95
	TIV-2	44	38	95	92

		Seroconversion		% ≥ 1:40 Day 22	
Strain	Group	%	LL 95% CI*	%	LL 95% CI*
B/Brisbane/3/2007	D-QIV	56	53	99	98
	TIV-1	42	37	99	97
	TIV-2	58	51	100	99

*CI = confidence interval
Source: BLA 125127/ SN 513, CSR D-QIV 008, Supplement 35, 36 p 226-228

The percentage of subjects with seroconversion and the percentage of subjects achieving an HI antibody titer ≥ 1:40 met the CBER criteria for demonstration of immunogenicity in the elderly (≥30% and ≥60% respectively) as described for accelerated approval of TIVs in FDA Guidance for Industry " Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines."

On review of safety results for subjects 65 years of age and older, there was no difference in the results for subjects who received Fluarix Quadrivalent and those who received TIV-1 or TIV-2. The most commonly reported adverse events in all arms for elderly subjects were solicited adverse reactions. The most frequently reported local solicited adverse reaction was pain at injection site (22%). The most frequently reported systemic solicited adverse reactions were fatigue (10%), muscle ache (10%) and headache (10%). The percentage of subjects reporting unsolicited AEs in the 21 Days post-vaccination was 11% in Fluarix Quadrivalent arm, 10% in TIV-1 arm and 15% in TIV-2 arm. The percentage of subjects with SAEs was less than 1 % in all arms.

10. CONCLUSIONS

The clinical data submitted in this sBLA support the safety and immunogenicity of Fluarix Quadrivalent when administered to subjects 3 years of age and older. The clinical recommendation for the traditional approval of Fluarix Quadrivalent is based on the demonstration of non-inferiority for the three influenza strains included in the currently licensed Fluarix vaccine and superiority for the B strain not included in the trivalent vaccine. Data from four studies support the safety in subjects 3-17 years of age as well as in older adults. Mild local injection site reactions, muscle aches and headache were reported in subjects 6 years of age and older and drowsiness, irritability and loss of appetite in subjects less than 6 years of age. Overall, in this reviewer's opinion, no safety concerns have been identified.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Influenza typically causes annual epidemics during the late fall through the early spring. • Severity of disease (rates of hospitalization and death) is worst in the elderly, children younger than 2 years of age, and individuals with medical conditions that place them at increased risk for complications. • The number of hospitalizations and deaths due to influenza varies each year. The CDC has reported a range of 3,000 to 49,000 deaths per year in the US due to influenza in the 30 years prior to 2007.	• Considerable morbidity and mortality is associated with yearly influenza epidemics. • Influenza vaccines are the most effective way of preventing morbidity and mortality due to influenza.
Unmet Medical Need	• There are currently eight trivalent, inactivated vaccines licensed in the U.S. for prevention of seasonal influenza in adults: Fluzone™, Fluzone HD™, Fluvirin™, Fluarix™, Afluria™, FluLaval™, Agriflu™ and Flucelvax™. There is also a live attenuated trivalent vaccine, FluMist, licensed in the U.S and a live attenuated quadrivalent vaccine FluMist Quadrivalent. • There are two distinct lineages of influenza B virus. Influenza B viruses from both lineages have circulated during the influenza season on several occasions. The B strain recommended for use in the yearly vaccine has been matched to the main circulating influenza B strain only in one-half of the influenza seasons in the last eight years. • Of the influenza B viruses tested in the 2011-2012 season, 51% belonged to the strain not included in the vaccine	• Fluarix Quadrivalent would be the first IM Quadrivalent inactivated influenza vaccine licensed in the U.S. • It will be the first quadrivalent inactivated influenza vaccine appropriate for use in persons over 3 years old with asthma or history of recurrent wheezing.
Clinical Benefit	• Vaccine non-inferiority and superiority for the additional B strain was demonstrated in a randomized placebo-controlled trial of 4656 adults from 18 years of age and older and 2738 pediatric patients age 3-17 years of age based on immunogenicity. Clinical benefit is inferred from Fluarix.	• Benefit was demonstrated in a large appropriately designed immunogenicity trial.
Risk	• The most commonly reported adverse events associated with Fluarix Quadrivalent were pain at the injection site and muscle aches and headache in subjects 6 years of age and older and drowsiness, irritability and loss of appetite in subjects less than 6 years of age.	• The most common safety risks are minor adverse reactions that are typically mild and resolve in several Days after vaccination. • The adverse event of hypersensitivity was treated with steroid and required hospitalization for one Day. The report of only 1 allergic type of AE does not represent an increased concern over other approved vaccine.
Risk Management	• The most frequently reported risk of vaccination with Fluarix Quadrivalent at the injection site were mild and resolved within Days. These will be described in the package insert.	• The package insert will reflect the safety risks reported in the studies of Fluarix Quadrivalent

11.2 Risk-Benefit Summary and Assessment

The data submitted in this application support the clinical immunogenicity of Fluarix Quadrivalent against the 2 influenza A subtype viruses and 2 influenza B lineage viruses. Fluarix Quadrivalent would be the first quadrivalent influenza vaccine licensed for intramuscular use in the U.S. This would provide a quadrivalent influenza vaccine for persons 3 years of age and older and also for persons with asthma or recurrent wheezing.

The most common risk associated with Fluarix Quadrivalent is pain at the injection site and muscle aches and headache in subjects 6 years of age and older and drowsiness, irritability and loss of appetite in subjects less than 6 years of age. Overall these AEs are mild and easily tolerated. There was on AE of hypersensitivity which required hospitalization and resolved with steroid treatment; however, this adverse event occurred 38 Days post-vaccination and is unlikely to be related to Fluarix Quadrivalent. The risk of an allergic reaction is observed with multiple vaccines, including the influenza vaccines already licensed in the U.S. Therefore the risk of one allergic reaction to Fluarix Quadrivalent is low and does not appear to be any greater than with other influenza vaccine.

Clinical lot consistency was demonstrated for this vaccine.

In the opinion of this clinical reviewer the benefits of the prevention of additional influenza disease with inclusion of two influenza B strains of different lineages, outweigh the risks of mild adverse events and rare allergic reactions.

11.3 Discussion of Regulatory Options

In the opinion of this reviewer, the immunogenicity and safety data support the traditional approval of Fluarix Quadrivalent in individuals 3 years of age and older..

11.4 Recommendations on Regulatory Actions

The clinical immunogenicity and safety data submitted in this application support the approval of this supplemental BLA.

11.5 Labeling Review and Recommendations

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

- The amount of immunogenicity and safety data from the Fluarix and Fluarix Quadrivalent studies included in the package insert.

11.6 Recommendations on Postmarketing Actions

The applicant initiated plans for a clinical endpoint efficacy study, D-QIV-004, in children age 6 through 35 months. The trial was initiated in October 2011 and data are expected to be available in 2013.

The applicant has agreed to establish a pregnancy registry as a postmarketing commitment.