Application Type	Supplemental Biologics License Application
STN	125163/254
CBER Received Date	October 18, 2012
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Division / Office	DVRPA/OVRR
Priority Review	No
Reviewer Names	Melisse Baylor, MD Roshan Ramanathan, MD, MPH
Review Completion Date / Stamped Date	August 16, 2013
Supervisory Concurrence	Jeff Roberts, MD
Applicant	ID Biomedical Corporation of Quebec (a subsidiary of GlaxoSmithKline Biologicals)
Established Name	Influenza Vaccine
(Proposed) Trade Name	FluLaval
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	Trivalent, split-virion, inactivated influenza virus vaccine provided in multi-dose vials containing thimerosal as preservative
Dosage Form(s) and Route(s) of Administration	Suspension for injection available in 5 mL multi-dose vials containing ten 0.5 mL doses to be administered by intramuscular injection
Dosing Regimen	In children 3 through 8 years of age who have not been previously vaccinated with influenza vaccine, two doses (0.5 mL) administered at least 4 weeks apart In children 3 through 8 years of age who have been previously vaccinated with influenza vaccine in a previous season, one 0.5 mL dose In individuals 9 years of age and older, one 0.5 mL dose
Indication(s) and Intended Population(s)	Active immunization against influenza disease caused by the 2 influenza virus subtypes A and the influenza B type contained in the vaccine. FluLaval is approved for use in persons 3 years of age and older.

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GLOSSARY

ACIP	Advisory Committee on Immunization Practices
AE	adverse event
ATP	according to protocol
BLA	biologics license application
CDC	Centers for Disease Control
CHMP	Committee for Medical Products for Human Use (EMA)
CI	confidence interval
CFR	Code of Federal Regulation
CMC	chemistry, manufacturing, and controls
CRF	case report form
eCTD	electronic Common Technical Document
EMA	European Medicines Agency
ELISA	Enzyme-Linked Immunosorbent Assay
ES	Executive Summary
FDAAA	Food and Drug Administration Amendments Act of 2007
GMR	geometric mean ratio
GMT	geometric mean titer
GRMP	good review management principles
GSK	GlaxoSmithKline Biologicals
HA	hemagglutinin
HAI	hemagglutinin inhibition assay
HI	hemagglutinin inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ILI	influenza like illness
IND	investigational new drug application
ISE	integrated summary of efficacy
ISS	integrated summary of safety
ITT	intent-to-treat
LB	lower bound
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
NCT	National Clinical Trials
N/E	non-evaluable
PI	package insert
pIMD	potential immune-mediated disease
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PREA	Pediatric Research Equity Act
REMS	risk evaluation and mitigation strategy
QIV	quadrivalent influenza vaccine
Q-QIV	quadrivalent formulation of FluLaval
RMS/BLA	regulatory management system for the biologics license application

RT-PCR	reverse-transcribed polymerase chain reaction
SAE	serious adverse event
sBLA	supplement to a Biologics License Application
SCR	seroconversion rate
(b)(4)	-------(b)(4)-------
TIV	trivalent influenza vaccine
VE	vaccine efficacy

1. Executive Summary

FluLaval is a trivalent, split-virion, inactivated, seasonal influenza virus vaccine. The current indication is "for active immunization against influenza disease caused by influenza virus subtypes A and type B contained in this vaccine. FluLaval is approved for use in persons 18 years of age and older."

With this supplement to the Biologics License Application (sBLA) for Flulaval, the applicant seeks to extend approved usage to children as young as 3 years of age. The supplement also fulfills two regulatory requirements. The first is the Pediatric Research Equity Act (PREA) requirement that applicants assess the safety and effectiveness of the drug or the biological product for the claimed indication(s) in all relevant pediatric subpopulations. Clinical study FLU-Q-TIV-(b)(4)-008, an immunogenicity and safety study comparing the trivalent formulation of Flulaval to a trivalent influenza vaccine licensed in children was conducted in a population 3 through 17 years of age. This study addresses the PREA requirement with regard to the TIV formulation in children ≥3 years of age. A separate study in children 6 through 35 months of age is ongoing (see below).

The second regulatory requirement addressed by this sBLA is the requirement to conduct post-approval study(ies) to verify and describe the anticipated clinical benefit of a product licensed under the accelerated approval regulations. FluLaval was originally licensed in the United States under the accelerated approval regulations (21 CFR 601.41). In the studies to support the original approval of FluLaval, antibody response was analyzed using serum hemagglutination inhibition (HI) titers as a surrogate endpoint that was considered reasonably likely to predict clinical benefit. Products approved under accelerated approval regulations are subject to the requirement to study the product further, to verify and describe the clinical benefit. To address this requirement, a clinical study evaluating the efficacy of FluLaval in preventing culture-confirmed influenza disease was conducted among adults age 18 through 49 years of age. However, results from that study did not provide sufficient evidence of clinical benefit to satisfy the requirements for full traditional approval. Of note, the attack rate for culture-confirmed, antigenically matched strains was lower than expected, contributing to a wide confidence interval for the estimate of vaccine efficacy. Results from this study (NCT00216242) were included in the FluLaval label. Subsequently, the applicant conducted a clinical endpoint efficacy study of a quadrivalent formulation of FluLaval in children to support the traditional approval of both the quadrivalent and trivalent formulations of FluLaval. That study, FLU-Q-QIV-006, evaluated the safety and efficacy of FluLaval Quadrivalent in preventing virologically-confirmed influenza illness among children 3 through 8 years of age. Results of study FLU-Q-QIV-006 are relevant for the trivalent formulation of FluLaval; because FluLaval and FluLaval Quadrivalent are manufactured using the same processes, and they contain overlapping components, including two influenza subtype A antigens and one influenza type B antigen. In pre-BLA meetings, CBER agreed that, if successful, results of this study would support the traditional approval of both FluLaval and FluLaval Quadrivalent.

Therefore, ID Biomedical has submitted in this sBLA, study FLU-Q-TIV-(b)(4)-008 to extend the indication for use to 3 years of age and older, and study FLU-Q-QIV-006 to support traditional approval for FluLaval, thus addressing PREA and accelerated approval requirements, respectively.

In Study FLU-Q-TIV-(b)(4)-008, a total of 2116 subjects from 3 through 17 years of age (1055 in the FluLaval group and 1061 in the active comparator group) were enrolled and vaccinated. The HI antibody responses to FluLaval and the licensed comparator vaccine, Fluzone® (Sanofi Pasteur), were evaluated by calculation of the ratio of the post-vaccination geometric mean titers (GMTs) and by the difference in seroconversion rates (SCR). Non-inferiority would be demonstrated: 1) if the upper bound of the 95% confidence interval for GMT ratio was 1.5 or less for all three influenza strains contained in the vaccine, and 2) if the upper bound of the 95% confidence interval for the difference in seroconversion rate was 10% or less for all three influenza strains contained in the vaccine. The pre-defined non-inferiority criteria were met for both GMT ratios and seroconversion rates for all three influenza strains.

The most commonly reported adverse reaction after vaccination with FluLaval or with Fluzone was pain at the injection site. Pain was reported in 59% and 57% of subjects in the FluLaval and Fluzone groups, respectively. However, pain was generally mild and self-limited; Grade 3 pain was reported in only 2.5% and 2.7% of subjects in the FluLaval and Fluzone groups, respectively. Unsolicited adverse events were reported in 42% of subjects who received FluLaval and in 41% who received Fluzone. Unsolicited adverse events were consistent with common illnesses seen in a pediatric population; the most frequently reported unsolicited adverse events in both groups were cough, upper respiratory tract infection, and pyrexia. Serious adverse events were reported in less than 1% of subjects in both treatment groups. In the opinion of this reviewer, none of the serious adverse events were definitively related to FluLaval.

Vaccine efficacy was 55.4% with a lower bound 95% confidence interval of 39.1%; these results met the protocol-defined criterion for demonstration of efficacy. Therefore, in the opinion of this reviewer, these results support the traditional approval of FluLaval.

The most commonly reported adverse reaction in this study was pain at the injection site, which was reported in 39% of subjects who received FluLaval QIV compared with 28% who received Havrix. Grade 3 pain was reported in only 0.9% and 0.7% of subjects in the FluLaval and Havrix groups, respectively. Other adverse reactions reported in 10% or more subjects in the Flulaval group were muscle aches (12%) and headache (11%). These adverse reactions were usually mild and self-limited. Unsolicited adverse events were reported in 33% of subjects in both treatment groups; serious adverse events were uncommon and reported in <1% of subjects within 28 days of vaccination in both groups. The types of unsolicited adverse events and serious adverse events were consistent with illnesses observed in children.

For children age 3 years and older, PREA requirements are addressed by safety and immunogenicity data from Study FLU-Q-TIV-(b)(4)-008. The PREA requirement for studies in children ages 0 to <6 months were waived, because vaccination in this age group provides 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 under 6 months of age. The remaining age group required to be studied under PREA is 6 to 36 months of age. The applicant has committed to

conduct a safety and immunogenicity study in this age group comparing FluLaval Quadrivalent to a U.S.-licensed comparator vaccine.

No safety signals were identified in the review of the two studies submitted in this Supplement. The applicant submitted a pharmacovigilance plan to monitor adverse events observed post-marketing. The plan includes a pregnancy registry that will evaluate maternal and neonatal outcomes after use of Flulaval during pregnancy. There are no targeted safety studies planned for FluLaval. This plan was acceptable to the reviewers from the Division of Epidemiology.

In conclusion, it is this reviewer's opinion that the data submitted by the applicant in this sBLA support the approval of FluLaval for the active immunization of persons 3 years of age and older against influenza disease caused by virus subtypes A and type B contained in the vaccine. In addition, the efficacy results support the traditional approval of FluLaval. The recommendation for the approval of FluLaval in pediatric patients is based on the non-inferior HI antibody responses when FluLaval was compared to a U.S.-licensed influenza vaccine, vaccine efficacy as demonstrated in the study of the quadrivalent formulation of FluLaval, and the acceptable safety profile, in which most adverse reactions were mild and self-limited.

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. During the years 1990-1999, influenza infection was responsible for an average of 36,000 deaths per year in the United States. The rates of infection are highest among children; serious illness and death are reported more frequently among children with chronic underlying medical conditions that place them at increased risk of complications. Influenza vaccination is the primary method for preventing influenza illness and its severe complications. In certain circumstances, antiviral medication can be an important adjunct to the vaccine for prevention and control of influenza.

The Advisory Committee on Immunization Practices (ACIP) recommends annual vaccination against seasonal influenza in all individuals 6 months of age and older. The ACIP recommendations also support additional efforts or programs to focus on vaccination of persons at higher risk for influenza-related complications, which includes but is not limited to persons greater than or equal to 50 years of age, persons with chronic medical conditions, children aged 6 months of age and older, and health care workers.

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

Prevention of influenza disease can be achieved through vaccination or the use of antiviral medication. Two classes of antivirals against influenza, the adamantanes and the neuraminidase inhibitors, have been approved for both treatment and prevention (pre-exposure chemoprophylaxis). The adamantane class, composed of the drugs amantadine and rimantadine, has been in use since the 1970s, but is no longer recommended due to widespread resistance in recent years among circulating influenza virus strains. Among neuraminidase inhibitors, zanamivir and oseltamivir are currently approved. Zanamivir is a powder delivered by inhalation, while

oseltamivir is administered orally. While this drug class is currently effective against seasonal influenza viruses, resistance has developed sporadically. Resistance usually results in some loss of viral fitness, thus limiting their spread. However, a seasonal A/H1N1 strain resistant to oseltamivir circulated widely during the 2008-09 influenza season with no loss of transmissibility or virulence, highlighting the vulnerability of this method of prevention.

Non-pharmaceutical preventive interventions for seasonal outbreaks and pandemics include hand hygiene practices, personal protective equipment and other isolation precautions in clinical settings, and social distancing.

2.3 Safety and Efficacy of Pharmacologically Related Products

Influenza vaccines have been available since the 1940s. There are currently four trivalent, inactivated, split-virion vaccines licensed in the U.S. for prevention of seasonal influenza in children. Fluzone is approved for use in children 6 months of age and older, Fluarix is approved for use in children three years of age and older, Fluvirin is approved for use in children four years of age and older, and Afluria is approved for use in children five years of age and older. There is also a live, attenuated intranasal vaccine (Flumist) approved for use in children 2 years of age and older. In addition, quadrivalent formulations of Fluzone, Fluarix, and FluMist are licensed for use in children and adults in the United States.

The clinical efficacy of trivalent influenza vaccines in prospective, randomized, controlled trials submitted to support traditional approval has been as high as 84%. However, most of these trials have been conducted in adults.

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

Serious adverse events associated with influenza vaccination are uncommon. Hypersensitivity reactions, including anaphylaxis, have been reported after influenza vaccination. These reactions have been uncommon (0-10 per million doses vaccine). Increased rates of Guillain-Barré syndrome (GBS), a rare neurological disorder (10-20 cases per 1 million adult population) characterized by ascending paralysis, were reported during the swine influenza virus vaccination campaign of 1976. Observational studies since then have identified an increased risk of at most 1 additional GBS case per million vaccinated persons associated with seasonal influenza vaccines.

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

FluLaval was first licensed in Canada in 1992 and is now marketed in 16 countries. According to the Division of Epidemiology reviewer, Dr. Zinderman, neither the applicant nor FDA have identified any safety signal specific to FluLaval since U.S. approval. There have been no actions taken for safety including no withdraws, rejections, suspension or failure to obtain a renewal of Marketing Authorization since the approval.

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

FluLaval was licensed on October 5, 2006 for the prevention of influenza subtypes A and type B contained in the vaccine under the accelerated approval regulations; the approval was based on the immune response elicited by FluLaval in clinical studies in adults. Since products approved under the accelerated approval regulations, 21CFR601.41, require further studies that are adequate and

well controlled to verify and describe clinical benefit, a clinical endpoint efficacy study (IDB-707-106; NCT00216242) was conducted in adults 18 through 49 years of age. In this study, the efficacy against culture-confirmed, antigenically matched strains was 46.3%, with a lower limit of the one-sided 97.5% confidence interval (CI) of 9.8%. Because the pre-specified success criterion for the lower limit of the CI was ≥35%, vaccine efficacy was not demonstrated according to the pre-defined criteria; although it was noted that the 1.2% attack rate in the placebo group for culture-confirmed, antigenically matched strains was lower than expected, contributing to a wide confidence interval for the estimate of vaccine efficacy.

Traditional approval based on the results of IDB-707-106 was not granted. After discussions with CBER, the applicant agreed to conduct a clinical endpoint study of the quadrivalent formulation of FluLaval; CBER agreed that such a study would support the traditional approval of both the trivalent and quadrivalent formulations of FluLaval, because the two formulations are manufactured according to the same process . The study protocol was submitted on August 20, 2010. The Clinical Study Report for the study was submitted concurrently with this supplement in sBLA 125163, submission number 253. The review of that study (FLU-Q-QIV-006) is included in this review.

The study protocol for FLU-Q-TIV-(b)(4)-008 was submitted in 2009. The study results were first submitted to CBER in 2011. On January 20, 2012, the applicant was informed that traditional approval of FluLaval would be required before the age indication for FluLaval could be lowered to include children. There was no pre-BLA meeting for this supplement.

2.6 Other Relevant Background Information

Not applicable

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.

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.

Four clinical sites in Study FLU–Q-TIV-(b)(4)-008 were inspected by investigators from the Division of Inspections and Surveillance. No problems that would impact the study results were identified.

3.3 Financial Disclosures

Covered clinical study (name and/or number):FLU-Q-TIV-(b)(4)-008

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 234		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 233		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

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

Data from previous submissions demonstrated that the manufacturing process is well controlled with appropriate validations, quality control testing, and stability data. No additional CMC information was required to be submitted with this application.

4.2 Assay Validation

The assays used in this supplement were reviewed as part of BLA 125163, Supplement 253 for the quadrivalent formulation of FluLaval.

4.3 Nonclinical Pharmacology/Toxicology

Results from two reproductive and developmental toxicology studies 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 an immune response that can be quantified by elevation in Hemagglutination Inhibition (HI) antibody titers. Specific levels of antibody have not been absolutely correlated with protection from influenza illness. In some studies and meta-analyses, 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)

Not applicable

4.4.3 Human Pharmacokinetics (PK)

Not applicable

4.5 Statistical

Please see Dr. Ahnn's review. Dr. Ahnn concluded that Study FLU-Q-TIV-(b)(4)-008 was conducted as pre-specified and that the primary immunogenicity objective was met. In addition, he concluded that FluLaval (b)(4) and Fluzone appear to have similar safety profiles.

4.6 Pharmacovigilance

Please see Dr. Zinderman's review. Dr. Zinderman concluded that there was no safety signal requiring additional study and that routine pharmacovigilance was acceptable.

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

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

5.1 Review Strategy

The primary focus of this review was on the pivotal study, FLU-Q-TIV-(b)(4)-008, which was an immunogenicity and safety study comparing FluLaval (b)(4) to Fluzone in children from 3 through 17 years of age. In addition, the results of FLU-Q-QIV-006 were included in this review for support of traditional approval of FluLaval. Study FLU-Q-QIV-006 was also submitted as the primary

support of the safety and efficacy of FluLaval Quadrivalent and was included in sBLA 125163/253. This study was reviewed in detail by Dr. Roshan Ramanathan under sBLA 125163/254. For convenience, Dr. Ramanathan's review of FLU-Q-QIV-006 is repeated verbatim in this clinical review.

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

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

5.3 Table of Studies/Clinical Trials

The number of subjects listed in the table below represents the total number of subjects enrolled in the clinical studies included in this BLA, not the number of subjects receiving FluLaval or FluLaval Quadrivalent.

Study	Type of clinical trial	Control	Total # Subjects	Age (yrs)	Country
FLU-Q-TIV-(b)(4)-008	Randomized, observer blind, immunogenicity and safety	Fluzone	2116	3-17	US
FLU-Q-QIV-006	Randomized, observer blind, clinical efficacy	Havrix	5168	3-8	Bangladesh, Dominican Republic, Honduras, Lebanon, Panama, Philippines, Thailand, Turkey

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.

5.4.2 External Consults/Collaborations

There were no external consults or collaborations for this application.

5.5 Literature Reviewed (if applicable)

Not applicable

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1 – FLU-Q-TIV-(b)(4)-008

A Phase III, observer-blind, randomized study to evaluate the immunogenicity and safety of FluLaval --------(b)(4)-------- (GSK Biologicals) compared with Fluzone® (Sanofi-Pasteur Inc.) administered intramuscularly in children 3 to 17 years of age in the United States

6.1.1 Objectives (Primary, Secondary, etc)

The primary objective was to demonstrate the immunological non-inferiority, in terms of Geometric Mean Titer (GMT) and Seroconversion Rate (SCR), of FluLaval ---------(b)(4)---------- versus Fluzone in children 3 to 17 years of age.
The secondary objectives were:

- To describe the immunogenicity of FluLaval (b)(4) and Fluzone for all subjects and for the age subgroups, 3-4 years, 5-8 years, and 9-17 years using GMTs, seroconversion rates, seroconversion factors, and percentage of subjects with HI titers ≥ 1:40, and
- To evaluate safety and reactogenicity of FluLaval and Fluzone.

6.1.2 Design Overview

Study FLU-Q-TIV-(b)(4)-008 was a Phase III immunogenicity and safety study in healthy subjects from 3 through 17 years of age. Subjects were stratified in a 1:1:1 ratio by age subgroup, 3-4 years, 5-8 years, and 9-17 years, and randomized in a 1:1 ratio to receive FluLaval (b)(4) or Fluzone. Primed subjects received a single 0.5 mL dose administered intramuscularly in the deltoid muscle of the non-dominant arm on Day 0. Unprimed subjects received two dose administered on Days 0 and 28. Subjects from 3 through 8 years were considered primed if they had previously received two doses of influenza vaccine in a single influenza season. Subjects from 3 through 8 years were considered unprimed if they had not received any seasonal influenza immunization in the past or had received only one dose of vaccine for the first time in the last influenza season. All subjects 9 to 17 years of age were considered primed and received a single dose of study vaccine regardless of vaccination history.

Reviewer comment: Fluzone is approved in the U.S. for use in individuals 6 months of age and older and was an appropriate control for this study.

6.1.3 Population

The study enrolled healthy children who were 3 through 17 years of age at the time of the first vaccination. Individuals were excluded for any of the following: receipt of a 2009-2010 seasonal influenza vaccine outside of the study, history of hypersensitivity to any vaccine, history of any reaction likely to be exacerbated by any component of the study vaccine, history of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine, acute disease or fever (≥38° C) at the time of enrollment, or immunosuppression or receipt of immunosuppressive drugs within 6 months. Females of child bearing potential had to agree to practice adequate contraception as defined in the study protocol. Females of child bearing potential had to have a negative pregnancy test prior to receipt of study vaccine.

Study subjects were allowed to receive routine childhood vaccinations or recommended pandemic influenza vaccine during study participation.

Reviewer comment: The study was conducted during the 2009-2010 influenza season, when the H1N1v pandemic influenza virus was circulating. At the time of the study, the Advisory Committee on Immunization Practices had recommended vaccination against pandemic H1N1 for U.S. children 6 months of age and older. Therefore, study subjects were allowed to be vaccinated against H1N1v pandemic influenza while participating in the study. In addition, previous receipt or intended receipt of the vaccine for the prevention of influenza due to H1N1v was used as a minimization factor.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Study vaccine was administered intramuscularly in the deltoid muscle of the non-dominant arm. Primed subjects received a single 0.5 mL dose on Day 0. Unprimed subjects received two doses administered 28 days apart (Days 0 and 28).

FluLaval (b)(4) contained a total of 45 µg of HA per 5 mL dose. It contained the three influenza strains recommended by WHO and CDC/CBER for the 2009-2010 influenza season in the Northern Hemisphere. FluLaval contained 15 µg of each of the following:
H1N1 strain: A/Brisbane/59/2007,
H3N2 strain: A/Uruguay/716/2007, and
B strain: B/Brisbane/60/2008.
----------(b)(4)----------.

Reviewer comment: Please see the Chemistry review for a discussion of the FluLaval manufacturing process. ----------(b)(4)----------.

Commercially-available Fluzone was used as the control. Fluzone was standardized according to USPHS requirements. Fluzone also contained a total of 45 µg of HA per 5 mL dose with 15 µg of each of the same influenza strains as FluLaval (b)(4).

6.1.5 Directions for Use

Not applicable

6.1.6 Sites and Centers

The study was conducted under IND 11016 in 30 centers in the United States.

6.1.7 Surveillance/Monitoring

Unprimed subjects 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 history-directed physical examination was performed on Day 0 and repeated if necessary at subsequent visits. Body

temperature was measured prior to 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 legal representative after vaccination. The parent or legal representative was instructed on how to complete the diary card and when to return the diary card.

Information on solicited adverse reactions was collected for four days after vaccination (day of vaccination and subsequent three days). The solicited local adverse reactions followed were pain, redness, and swelling at the injection site. The solicited systemic adverse reactions followed in subjects younger than 5 years of age were drowsiness, fever, irritability/fussiness, and loss of appetite. The solicited systemic adverse reactions followed in subjects 5 years of age and older were fatigue/tiredness, fever, headache, joint pain, muscle aches (widespread or general), and shivering (chills). Temperature was to be measured every night and if the subject might be feverish. The highest temperature in each 24 hour period was to be entered onto the Diary Card.

Information on unsolicited adverse events (AEs) was collected for 28 days after vaccination. Information on medically attended AEs and serious AEs was collected during the entire study period. Medically attended visits were defined as hospitalization, emergency room visit, or a visit to medical personnel.

6.1.8 Endpoints and Criteria for Study Success

The primary endpoint was the humoral immune response to each of the influenza vaccines. Blood was obtained for immune response assessment on Day 0 prior to vaccination and again post-vaccination, on Day 28 for primed subjects and those older than 9 years of age and on Day 56 for unprimed subjects younger than 9 years of age.

Serum antibody levels were measured using an in-house assay at the GSK Biologicals laboratory. Serum hemagglutination inhibiting (HI) antibodies were used to calculate GMTs of HI antibody titers and SCR.

The primary objective was to demonstrate the immunological non-inferiority of FluLaval (b)(4) versus Fluzone in children 3 to 17 years of age. The HI antibodies were analyzed using Geometric Mean Titers (GMTs) and seroconversion rates (SCR). Seroconversion rate was defined as the percentage of subjects with either a pre-vaccination HI titer <1:10 and a post-vaccination titer ≥ 1:40 or a pre-vaccination titer ≥ 1:10 and a fourfold or higher increase in post-vaccination titer. Immunological non-inferiority would be demonstrated if:

- The upper limit of the two-sided 95% confidence interval (CI) of the GMT ratio post-vaccination (Fluzone/FluLaval (b)(4)) did not exceed 1.5 for the three strains and
- The upper limit of the two-sided 95% confidence interval for the difference in seroconversion rates at post-vaccination (Fluzone – FluLaval (b)(4)) did not exceed 10% for all three strains.

The secondary endpoints included evaluation of the immune response in terms of HI antibodies using geometric mean reciprocal serum HI antibody titers, seroconversion rates, the percentage of subjects with HI titers ≥ 1:40 and seroconversion factors, defined as the fold increase in serum HI

GMTs post-vaccination compared to pre-vaccination. Seroconversion rates and the percentage of subjects with post-vaccination HI titers ≥ 1:40 were evaluated using CBER criteria for demonstration of immunogenicity of trivalent seasonal influenza vaccines in adults using the accelerated approval mechanism as described in the FDA Guidance for Industry, "Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines." Using these criteria, immunogenicity is demonstrated if:

- The lower bound 95% CI for the seroconversion rate for each influenza strain is ≥ 40% and
- The lower bound 95% for the percentage of subjects with post-vaccination HI titers ≥1:40 is ≥ 70%.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Subjects were stratified in a 1:1:1 ratio by age subgroup, 3-4 years, 5-8 years, and 9-17 years, and randomized in a 1:1 ratio to receive FluLaval (b)(4) or Fluzone. The randomization list was generated at GSK Biologicals, ---(b)(4)--- using a Statistic Analysis System® program Minimization factors for treatment allocation included had received H1N1v pandemic vaccine or intended to receive H1N1v pandemic vaccine, priming status.

The study was conducted in an observer-blind manner. The study personnel involved in preparation and administration of the study vaccine did not participate in any of the study clinical evaluation. Laboratory personnel responsible for serological testing were blinded to study treatment.

The study planned to enroll 2100 subjects with 1050 randomized to each of the two vaccine groups. With a 25% or less drop out/unevaluable rate, the statistical power to meet the primary study objective was 94.9%. See Section 6.1.9 for a description of the criteria needed to meet the primary endpoint.

The study populations for analyses were:

- The total vaccinated cohort (TVC) included all vaccinated subjects. The TVC for analysis of safety included all subjects with at least one vaccination documented, and the TVC for analysis of immunogenicity included all vaccinated subjects for whom immunogenicity endpoint measurements were available. The primary analysis of safety was performed using the TVC.
- The according-to-protocol (ATP) cohort for analysis of safety included all subjects who received at least one dose of the study vaccine to which they were randomized, who had sufficient data for a safety analysis, who had not received a vaccine forbidden in this protocol, for whom the administration site of the study vaccine was known, and for whom the randomization code had not been broken.
- The ATP cohort for analysis of immunogenicity included all evaluable subjects (who met entry criteria, complied with protocol procedures and intervals, and had no elimination criteria) for whom data concerning immunogenicity measures were available. The primary analysis of immunogenicity was to be performed using this population.

The statistical analysis of safety was descriptive. AEs were captured using MedDRA terminology.

6.1.10 Study Population and Disposition

The study was conducted at 30 centers in the United States. The first subject was enrolled on October 13, 2009. Safety follow-up was completed on June 17, 2010.

6.1.10.1 Populations Enrolled/Analyzed

See Section 6.1.9 for definitions of study populations.

A total of 2116 subjects were vaccinated and included in the Total Vaccinated Cohort; 1055 received FluLaval (b)(4) and 1061 received Fluzone.

6.1.10.1.1 Demographics

The mean age of subjects in the Total Vaccinated Cohort was 7.8 years; the median age was 7.0 years. Forty-seven percent of subjects were female. The majority (76%) of subjects was White/Caucasian; 11.6% were African American. No other race composed more than 1.6% of subjects. Twenty-six percent were of Hispanic or Latino ethnicity.

Demographic characteristics by age subgroup (3-4 years, 5-8 years, and 9-17 years) were also analyzed. Differences of 5% or more between the two treatment groups were observed for percentage of female subjects in the 3-4 year age group (54% in the FluLaval (b)(4) group and 47.5% in the Fluzone group), in the percentage of White Caucasians in the 5-8 year age group (78.7% in the FluLaval (b)(4) group and 71.5% in the Fluzone group), and in the percentage of African Americans in the 3-8 year age group (8.7% in the FluLaval group and 15.8% in the Fluzone group). Overall the demographic characteristics were similar for each of the three age groups.

The demographic characteristics of the ATP Cohort for Immunogenicity were comparable to those of the TVC.

Reviewer comment: When the entire study population was analyzed, baseline demographic characteristics were similar between the two study groups. There were some minor differences by treatment group when demographic characteristics were analyzed by age subgroup. However, overall the demographic characteristics were similar in the three age groups.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The percentage of subjects who had received a seasonal influenza vaccine in the previous three influenza seasons was 57% in the FluLaval (b)(4) group and 56% in the Fluzone group. The percentage of subjects who had been previously vaccinated against seasonal influenza varied by age subgroup and is shown in the following table.

Table 1: Study FLU-Q-TIV-(b)(4)-008 – Number and Percentage of Subjects who had Previously Received Influenza Vaccine by Treatment Group and Age Group

Age Subgroup	FluLaval (b)(4) N=1055	Fluzone N=1061
3-4 Years	215 (72%)	209 (71%)
5-8 Years	225 (58%)	207 (53%)
9-17 Years	158 (43%)	176 (47%)

Source: BLA 125163/ SN 254, Datasets WHINF, WDEMOG, and EXPOGN

Reviewer comment: The percentage of subjects who had previously been vaccinated against seasonal influenza was highest in the youngest age group, and the percentage in the middle 5 to 8 year age group was less than that in the older 9 to 17 year age group. The percentages by age group were similar in each treatment group and should not have affected the analysis of immunogenicity by age. See Section 6.1.11.2 for the results of immunogenicity by age for a discussion of results by age group.

The number of subjects who had received a pandemic influenza vaccine prior to study entry was small: 12 subjects (1.1%) in the FluLaval (b)(4) group and 18 (1.7%) in the Fluzone group. The percentage of subjects who received a H1N1v pandemic vaccine during study participation, after vaccination with study vaccine, and prior to measurement of antibody response 28 days after the last study vaccinated was 27% in the FluLaval (b)(4) group and 28% in the Fluzone group.

The percentage of subjects who had been vaccinated against the circulating H1N1v pandemic strain was very low at baseline in both treatment groups. The percentage of subjects who were vaccinated prior during study participation, after vaccination with study vaccine but prior to measurement of antibody response to study vaccine was similar in the two treatment groups, and therefore, should not have biased the study results.

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

Table 2: FLU-Q-TIV-(b)(4)-008 – Study Subject Disposition
Total Vaccinated Cohort

	FluLaval (b)(4)	Fluzone	Total
Number of subjects vaccinated	1055	1061	2116
Number of subjects completing active phase	998	991	1989
Number of subjects discontinuing prematurely	57	70	127
Reasons for premature discontinuation			
Lost to follow-up	42	49	91
Consent withdrawn	7	17	24
Moved from study area	3	0	3
Other	5	4	9

Source: BLA 125163/ SN 254, Dataset WDROP.

Overall, there were 1989 subjects (94.0%) who completed the study; the percentage discontinuing the study prematurely in the FluLaval (b)(4) group was 5.4% and in the Fluzone group was 6.6%. The majority of subjects, who discontinued the study, were discontinued due to loss to follow-up. Of those, most (29 in the FluLaval (b)(4) group and 31 in the Fluzone group) were lost to follow-up after completion of study vaccination and final blood draw.

Reviewer comment: The percentage of subjects with premature study discontinuation was similar between the two study groups. The reasons for premature study discontinuation were also similar between the two study groups. Many of the premature discontinuations occurred after subjects had received study vaccine(s) and follow-up blood draw for serology. Overall, 6% of subjects

discontinued the study prematurely, which may suggest that an acceptable retention strategy was in place and/or that the vaccine tolerability was acceptable for subjects requiring two doses.

Of the 2116 subjects in the Total Vaccinated Cohort, 23 (0.7%) were excluded from the ATP safety cohort and 150 (7.1%) were excluded from the ATP immunogenicity cohort. The reasons for exclusion are shown in the following table.

Table 3. FLU Q-TIV-(b)(4)-008 – Reasons for Exclusion from the ATP Safety and Immunogenicity Cohorts

	FluLaval (b)(4)	Fluzone	Total
Total Vaccinated Cohort	1055	1061	2116
ATP cohort for safety	1046	1056	2102
Vaccine not administered according to protocol	6	4	10
Administration of forbidden vaccine	2	1	2
Randomization code broken	1	0	2
ATP Immunogenicity Cohort	987	979	1966
Serological data missing	31	50	81
Non-compliance with blood sampling schedule	24	23	47
Non-compliance with vaccination schedule	4	3	7
Protocol violation	0	1	1

Source: BLA 125163/ SN 254, CSR Q-TIV-(b)(4)-008, Table 15, page 17.

The majority of subjects in both treatment groups were included in the ATP safety cohort. Most subjects (93%) were also included in the ATP immunogenicity cohort the number of subjects excluded in the Fluzone group (82 or 7.7%) was similar to that in the FluLaval group (68 or 6.4%); however a larger number of Fluzone recipients (50) compared to FluLaval (b)(4) recipients (31) had missing serological data.

Reviewer comment: The majority of the subjects who were vaccinated were included in the ATP safety cohort and in the ATP immunogenicity cohort. The percentage of subjects included in each cohort was similar between the two treatment groups. There were more subjects in the Fluzone group with missing serological data compared to the FluLaval (b)(4) group, but the overall percentage of subjects with missing serological data was small in both groups (4.7% in the Fluzone group and 2.9% in the FluLaval (b)(4) group) and therefore, unlikely to bias study results.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The non-inferiority of FluLaval (b)(4) to Fluzone was determined by comparison of post-vaccination GMTs of HI antibodies at day 28 or day 49 for each vaccine strain and by comparison of the seroconversion rate post-vaccination. Results for this primary endpoint are shown in the following two tables.

Table 4: FLU-Q-TIV-(b)(4)-008 – Non-Inferiority Comparison of Post-Vaccination Geometric Mean Titers of HI Antibodies by Treatment Group (ATP immunogenicity Cohort)

	GMTs		Ratio GMTs Fluzone/FluLaval (b)(4) (UL 95% CI*)
	Fluzone N=978	FluLaval (b)(4) N=987	
A/Brisbane (H1N1)	347	337.5	1.03 (1.13)
A/Uruguay (H3N2)	453	433	1.05 (1.13)
B/Brisbane	204	219	0.93 (1.02)

* Upper limit of the 95% confidence interval
Source: BLA 125163/ SN 254, CSR Q-TIV-(b)(4)-008, Table 23, page 83.

As shown in the table above, the upper limits of the 95% confidence intervals were less than 1.5 for all three vaccine strains; therefore, the criteria for determining non-inferiority (upper limit of 95% CI ≤ 1.5) were met for all three vaccine strains.

Table 5: FLU-Q-TIV-(b)(4)-008 – Non-Inferiority Comparison of Post-Vaccination Seroconversion Rate by Treatment Group (ATP immunogenicity Cohort)

	GMTs		Seroconversion Rates Fluzone minus FluLaval (b)(4) (UL 95% CI*)
	Fluzone N=978	FluLaval (b)(4) N=987	
A/Brisbane (H1N1)	58%	60%	-1.60 (2.75)
A/Uruguay (H3N2)	66%	68%	-2.03 (2.12)
B/Brisbane	79%	81%	-2.42 (1.13)

* Upper limit of the 95% confidence interval
Source: BLA 125163/ SN 254, CSR Q-TIV-(b)(4)-008, Table 24, page 83.

The non-inferiority criteria were also met for seroconversion rate. The upper limits of the 95% confidence intervals were less than 10 for all three vaccine strains.

Reviewer comment: Non-inferiority of the antibody response to each of the three influenza strains in FluLaval (b)(4) compared to Fluzone, a U.S. licensed comparator, was demonstrated using both GMT ratios and differences in seroconversion rates. Therefore, the primary endpoint for the study was met.

6.1.11.2 Analyses of Secondary Endpoints

The secondary immunogenicity objectives were to describe the immunogenicity of FluLaval (b)(4) and Fluzone for all subjects and for the age subgroups using GMTs, seroconversion rates, seroconversion factors, and percentage of subjects with HI titers ≥ 1:40.

The baseline GMTs and the percentage of subjects with HI titers of 1:40 or higher at baseline are shown in the following table.

Table 6. FLU-Q-TIV-(b)(4)-008 – Baseline Geometric Mean Titers (GMTs) and Percentage of Subjects with HI Titers ≥ 1:40 at Baseline (ATP immunogenicity Cohort)

	FluLaval (b)(4) N=987		**Fluzone N=978**	
	GMTs	**% HI ≥ 1:40**	**GMTs**	**% HI ≥ 1:40**
A/Brisbane (H1N1)	46.0	64.8%	45.8	65.3%
A/Uruguay (H3N2)	57.1	68.5%	63.9	70.6%
B/Brisbane	16.6	36.4%	16.8	36.8%

Source: BLA 125163/ SN 254, CSR Q-TIV-(b)(4)-008, Table 25, 27, page 85, 87.

The baseline GMTs and the percentage of subjects with baseline HI titers of 1:40 or higher were similar in the FluLaval (b)(4) and Fluzone groups. The pre-vaccination GMTs and percentage of subjects with HI titers ≥ 1:40 were higher for the influenza A strains than the influenza B strains at baseline.

The baseline geometric mean titers by age group are shown in the following table.

Table 7. FLU-Q-TIV-(b)(4)-008 – Baseline Geometric Mean Titers (GMTs) at Baseline by Age Group (ATP immunogenicity Cohort)

	FluLaval (b)(4)	**Fluzone**
	GMTs	**GMTs**
3-4 Years	**N=275**	**N=260**
A/Brisbane (H1N1)	38.4	34.4
A/Uruguay (H3N2)	38.7	50.2
B/Brisbane	13.1	11.6
5-8 Years	**N=353**	**N=353**
A/Brisbane (H1N1)	40.2	41.4
A/Uruguay (H3N2)	78.5	78.1
B/Brisbane	16.2	16.9
9-17 Years	**N=359**	**N=365**
A/Brisbane (H1N1)	60.2	61.9
A/Uruguay (H3N2)	56.3	62.6
B/Brisbane	20.5	21.7

Source: BLA 125163/ SN 254, CSR Q-TIV-(b)(4)-008, Supplement 9, pages 145-146.

The baseline GMTs to each influenza antigen were similar between treatment groups in each age group.

Reviewer comment: Baseline GMTs were similar within age groups with the greatest difference for the GMTs to A/Uruguay of 11.9% between the FluLaval (b)(4) and Fluzone groups in the age 3-4 years of age group. In general, baseline GMTs increased with increasing age, which could be consistent with more natural exposure to different influenza strains or with receipt of more vaccines. However, as noted previously in this review, the percentage of subjects who had previously been vaccinated against influenza was substantially higher in the 3-4 year age group. These data suggest that either natural infection may result in a higher antibody response to influenza strains or young age may result in a decreased antibody response to vaccination.

The criteria used to evaluate immunogenicity of seasonal influenza vaccines among adults under the regulations for accelerated approval regulations are described in the FDA Guidance for Industry, "Clinical Data Needed to Support the Licensure of Trivalent Inactivated Influenza Vaccines." Per these guidelines, serum HI antibody responses are considered acceptable for accelerated approval (reasonably likely to predict clinical benefit) if the lower limit of the 95% confidence interval for post-vaccination seroconversion rate is 40% or greater for each vaccine strain, and if the percentage of subjects with post-vaccination HI titers ≥ 1:40 is 70% or greater for each vaccine strain. The seroconversion rate and the percentage of subjects of all subjects with post-vaccination antibody titers of 1:40 or greater are shown in the following table.

Table 8: FLU-Q-TIV-(b)(4)-008 - Seroconversion Rate and Percentage of Subjects with HI Titer Post-Vaccination of ≥ 1:40 (ATP Immunogenicity Cohort)

	FluLaval (b)(4) N=987		**Fluzone N=979**	
	SC* Rate	**LL 95% CI**	**SC* Rate**	**LL 95% CI**
A/Brisbane (H1N1)	59.8%	56.6%	58.2%	55.0%
A/Uruguay (H3N2)	68.2%	65.2%	66.2%	63.1%
B/Brisbane	81.1%	78.5%	78.6%	75.9%
	% ≥ 1:40	**LL 95% CI#**	**% ≥ 1:40**	**LL 95% CI**
A/Brisbane (H1N1)	98.2%	97.1%	98.6%	97.6%
A/Uruguay (H3N2)	98.3%	97.3%	99.4%	98.7%
B/Brisbane	94.8%	93.3%	94.5%	92.9%

*SC=seroconversion, #LL 95% CI=lower limit of 95% confidence interval
Source: BLA 125163/ SN 254, CSR Q-TIV-(b)(4)-008, Table 26, 27, page 86, 87.

As shown in the table above, applying the criteria described in the FDA Guidance for Industry, overall study results for FluLaval and for Fluzone met these criteria for all six endpoints.

Reviewer comment: Although the criteria for accelerated approval of a seasonal trivalent influenza vaccine were designed for use in adults, and the accelerated approval mechanism is not being used for this application; the results for FluLaval (b)(4) and for Fluzone met these criteria for demonstration of immunogenicity as described in the FDA Guidance and pre-specified in the study protocol. In addition, the results for percentage of subjects with post-vaccination HI titers ≥1:40 and for seroconversion rate were similar in the two treatment groups. The demonstration of immunogenicity using these criteria provides additional support for the effectiveness of FluLaval in children.

Antibody response was also measured by post-vaccination GMTs and by seroconversion factor. The results for these endpoints are shown in the following table.

Table 9. FLU-Q-TIV-(b)(4)-008 – Post-Vaccination Geometric Mean Titers (GMTs) and Seroconversion Factor (SCF)
(ATP immunogenicity Cohort)

	FluLaval (b)(4) N=987		Fluzone N=978	
	GMTs	**SCF***	**GMTs**	**SCF***
A/Brisbane (H1N1)	321	7.0	329	7.2
A/Uruguay (H3N2)	415	7.3	452	7.1
B/Brisbane	214	12.8	200	11.9

*SCF=seroconversion factor, defined as the fold increase in serum HI GMTs post-vaccination compared to pre-vaccination
Source: BLA 125163/ SN 254, CSR Q-TIV-(b)(4)-008, Table 25, 28, page 85, 87.

The geometric mean antibody titer increased from pre-vaccination to post-vaccination by 7.0 to 12.8 fold in the FluLaval (b)(4) group and by 7.1 to 11.9 in the Fluzone group.

Reviewer comment: GMTs post-vaccination were substantially higher for each influenza strain and in each treatment group. The fold increase was similar in the two treatment groups.

Subjects were stratified by age (3-4 years, 5-8 years and 9-17 years) as part of the randomization scheme. The analysis of immunogenicity by age subgroups was a secondary endpoint of the study. The results by age group for seroconversion rate and percentage of subjects with post-vaccination HI titer of 1:40 or higher are shown in the following tables.

Table 10: FLU-Q-QIV-008 - Seroconversion rate by Treatment Group and Age Group
(ATP Immunogenicity Cohort)

	FluLaval (b)(4)		Fluzone	
	SC Rate	**LL* 95% CI**	**SC Rate**	**LL* 95% CI**
3-4 Years				
A/Brisbane (H1N1)	58.5%	52.5%	68.1%	62.0%
A/Uruguay (H3N2)	73.8%	68.2%	73.1%	67.2%
B/Brisbane	82.5%	77.5%	82.3%	77.1%
5-8 Years				
A/Brisbane (H1N1)	59.8%	54.5%	54.1%	48.8%
A/Uruguay (H3N2)	66.0%	60.8%	64.6%	59.4%
B/Brisbane	81.9%	77.4%	83.0%	78.7%
9-17 Years				
A/Brisbane (H1N1)	60.7%	55.5%	55.1%	49.8%
A/Uruguay (H3N2)	66.0%	60.9%	62.7%	57.6%
B/Brisbane	79.1%	74.5%	71.8%	66.9%

* Lower limit of the 95% confidence interval
Source: BLA 125163/ SN 254, CSR Q-TIV-(b)(4)-008, Supplement 10, page 147-148.

Table 11: FLU-Q-QIV-008 - Percentage of Subjects with Post-Vaccination HI Titer ≥1:40 by Treatment Group and Age Group (ATP Immunogenicity Cohort)

	FluLaval (b)(4)		Fluzone	
	HI Titer≥1:40	**LL* 95% CI**	**HI Titer≥1:40**	**LL* 95% CI**
3-4 Years				
A/Brisbane (H1N1)	96.4%	93.4%	99.2%	97.2%
A/Uruguay (H3N2)	96.4%	93.4%	99.6%	97.9%
B/Brisbane	92.4%	88.6%	91.9%	87.9%
5-8 Years				
A/Brisbane (H1N1)	98.3%	96.3%	97.7%	95.6%
A/Uruguay (H3N2)	98.9%	97.1%	99.2%	97.5%
B/Brisbane	94.6%	91.7%	94.6%	91.7%
9-17 Years				
A/Brisbane (H1N1)	99.4%	98.0%	98.9%	97.2%
A/Uruguay (H3N2)	99.2%	97.6%	99.5%	98.0%
B/Brisbane	96.9%	94.6%	96.2%	93.6%

* Lower limit of the 95% confidence interval

Source: BLA 125163/ SN 254, CSR Q-TIV-(b)(4)-008, Supplement 11, page 148-149.

As shown in the tables above, in each of the age groups, the lower bound 95% confidence interval of the seroconversion rate for all three vaccine strains was greater than 40% in both treatment groups, e.g., met criteria described in the FDA Guidance. In addition, in all three age groups, the percentage of subjects with post-vaccination HI titers of 1:40 or higher to each of the influenza strains was greater than 70%, which also met the criteria for demonstration of immunogenicity. However, it must be noted that while the use of these criteria are not appropriate for the pediatric population and were not endpoints in the study, these criteria do provide an additional method for evaluation of antibody response.

Reviewer comment: The seroconversion rates and percentage of subjects with post-vaccination HI titers ≥ 1:40 were similar between groups within each of the age subgroups. Differences in seroconversion rates were observed; there was a 5% or greater difference noted in response to H1N1 antigen in each age group. Of note, the seroconversion rate was higher in the 5-8 year and 9-17 year age group in the FluLaval (b)(4) group and higher in the 3-4 year age group in the Fluzone group. There were only slight differences in the antibody response by age group.

6.1.11.3 Subpopulation Analyses

The analysis of immunogenicity by age subgroup was a secondary endpoint. Please see Section 6.1.11.2 for a discussion of the results by age. The results of analyses by gender and ethnicity are discussed in Section 7.0.

6.1.11.4 Dropouts and/or Discontinuations

Missing or non-evaluable immunogenicity and safety measurements were not replaced. The denominators for the measurements were the number of subjects with results for that particular data point and not all subjects vaccinated.

The analysis of immunogenicity was to be conducted using the ATP immunogenicity cohort. If more than 5% of subjects were excluded from the ATP immunogenicity cohort, the analysis was to be repeated using the total vaccinated cohort. Since 7% of subjects were excluded from the ATP immunogenicity cohort, this analysis was performed and is shown in the following tables.

Table 12: FLU-Q-TIV-(b)(4)-008 – Non-Inferiority Comparison of Post-Vaccination Geometric Mean Titers of HI Antibodies by Treatment Group (Total Vaccinated Cohort)

	GMTs		Ratio GMTs Fluzone/FluLaval (b)(4) (UL 95% CI*)
	Fluzone N=1010	FluLaval (b)(4) N=1022	
A/Brisbane (H1N1)	346.6	334.4	1.04 (1.13)
A/Uruguay (H3N2)	456.9	432.3	1.06 (1.15)
B/Brisbane	202.6	215.3	0.86 (1.03)

* Upper limit of the 95% confidence interval
Source: BLA 125163/ SN 254, CSR Q-TIV-(b)(4)-008, Supplement 26, page 158.

Table 13: FLU-Q-TIV-(b)(4)-008 – Non-Inferiority Comparison of Post-Vaccination Seroconversion Rate by Treatment Group (Total Vaccinated Cohort)

	GMTs		Ratio Seroconversion Rates Fluzone minus FluLaval (b)(4) (UL 95% CI*)
	Fluzone N=1010	FluLaval (b)(4) N=1022	
A/Brisbane (H1N1)	58.2%	59.6%	-1.37 (2.91)
A/Uruguay (H3N2)	66.1%	67.7%	-1.57 (2.52)
B/Brisbane	78.6%	81.1%	-5.99 (0.99)

* Upper limit of the 95% confidence interval
Source: BLA 125163/ SN 254, CSR Q-TIV-(b)(4)-008, Supplement 27, page 158.

As shown in these tables, the results met the criteria for demonstration of non-inferiority of FluLaval (b)(4) to Fluzone using the total vaccinated cohort.

Reviewer comment: The study was designed to handle missing data appropriately. The study also was designed to do additional analyses using the total vaccinated cohort if there were more than 5% of subjects missing from the ATP immunogenicity cohort. These additional analyses were performed and confirmed the immunogenicity results. Overall, 5% of subjects discontinued the study and 7% were excluded from the ATP cohort for immunogenicity, which is reasonable in a six month study of pediatric patients.

6.1.11.5 Exploratory and Post Hoc Analyses

As a post-hoc analysis, the applicant analyzed the immunogenicity response to the H1N1v pandemic virus in each treatment group. This analysis is shown in the following table.

Table 14. FLU-Q-TIV-(b)(4)-008 – Post-Vaccination Antibody Responses to H1N1v Pandemic Virus
(ATP Immunogenicity Cohort)

	GMT	% HI Titer ≥ 1:40	SCR*	SCF#
FluLaval (b)(4) N=987	28.7	50.5%	28.1%	2.6
Fluzone N=979	28.5	51.9%	27.3%	2.5

*SCR = seroconversion rate, #SCF = seroconversion factor
Source: BLA 125163/ SN 254, CSR Q-TIV-(b)(4)-008, Table 29, page 89.

The antibody responses to the H1N1v pandemic vaccine was similar in each of the treatment group.

Reviewer comment: Approximately 30% of subjects in each of the treatment groups had been vaccinated against the H1N1v pandemic virus prior to having immunogenicity responses measured (e.g. before entering the study or after study vaccination but before antibody response to study vaccine was measured); therefore, it is not surprising that the antibody responses were low. In addition, the antibody response was similar in each study group, and there was no evidence of interference of antibody response to the H1N1v by FluLaval compared to Fluzone.

6.1.12 Safety Analyses

6.1.12.1 Methods

The analysis of safety was performed on the Total Vaccinated Cohort, which included 2116 subjects; 1055 of whom received FluLaval (b)(4) and 1061 of whom received Fluzone.

6.1.12.2 Overview of Adverse Events

The percentage of subjects with any adverse event (solicited or unsolicited) reported during the first four days after vaccination (day of vaccination and subsequent three days) is shown in the following table.

Table 15. FLU-Q-TIV-(b)(4)-008 –Percentage of Subjects with Adverse Events (Solicited and Unsolicited) During the Four Days Post-Vaccination
(ATP Safety Cohort)

Type of Solicited Adverse Reaction	FluLaval (b)(4) N=1055	Fluzone N=1061
Any Adverse Event/Reaction	69%	66%
Any Grade 3 Adverse Event/Reaction	6.4%	6.2%
Any Systemic Adverse Event/ Reaction	45.5%	45%
Grade 3 Systemic Adverse Event/Reaction	4.6%	3.9%
Any Local Adverse Event/Reaction	59%	56%
Grade 3 Local Adverse Event/Reaction	2.7%	2.7%

Source: BLA 125163/ SN 254, CSR Q-TIV-(b)(4)-008, Tables 30-31, page 91

During the four days post-vaccination, local adverse events or reactions were reported more commonly than systemic adverse events. The percentage of subjects with any adverse event, any systemic adverse

event, or any local adverse event was similar between the two treatment groups. Grade 3 adverse events were uncommon in both treatment groups.

The percentages of subjects reporting individual solicited local adverse reactions are shown in the following table. These results are for overall results for each subject; therefore, the results include results for both doses of a two-dose series.

Table 16. FLU-Q-TIV-(b)(4)-008 –Percentage of Subjects with Individual Solicited Local Adverse Reactions during the Four Days Post-Vaccination (ATP Safety Cohort)

Type of Solicited Local Adverse Reaction	FluLaval (b)(4) N=1055	Fluzone N=1061
Any Pain	59%	57%
Grade 3 Pain	2.5%	2.7%
Any Redness	5.5%	5.2%
Grade 3 redness (>100 mm)	0.2%	0.1%
Any Swelling	4.9%	5.8%
Grade 3 Swelling (>100 mm)	0.1%	0

Source: BLA 125163/ SN 254, CSR Q-TIV-(b)(4)-008, Table 34, page 94.

Pain at the injection site was reported for more than one-half of the subjects in each group. Redness and swelling at the injection site were less common. Grade 3 solicited local adverse reactions were uncommon. The percentage of subjects with individual solicited local adverse reactions and with Grade 3 local adverse reactions was similar in the two treatment groups.

The percentages of subjects with solicited local adverse reactions by dose are shown in the following table.

Table 17. FLU-Q-TIV-(b)(4)-008 - Percentage of Subjects with Individual Solicited Local Adverse Reactions by Dose during the Four Days Post-Vaccination (ATP Safety Cohort)

	Dose 1		Dose 2	
Type of Solicited Local Adverse Reaction	**FluLaval (b)(4) N=1042**	**Fluzone N=1026**	**FluLaval (b)(4) N=396**	**Fluzone N=386**
Any Pain	56%	53%	44%	43%
Any Redness	4.0%	4.5%	4.8%	2.6%
Any Swelling	4.4%	4.9%	2.5%	3.1%

Source: BLA 125163/ SN 254, CSR Q-TIV-(b)(4)-008, Table 34, page 94.

The most commonly reported solicited local adverse reaction was pain at the injection site. The percentage of subjects with individual solicited adverse reactions was lower after the second dose of study vaccine compared to the first with the exception of redness at the injection site in the FluLaval (b)(4) group.

Reviewer comment: The percentage of subjects with pain at the injection site was similar in the two treatment groups. The reason that redness at the injection site decreased in the Fluzone group after the second dose compared to the first dose but increased after the second dose of FluLaval (b)(4) is unclear.

The individual solicited systemic adverse reactions followed varied by subject age. The percentage with solicited systemic adverse reactions for subjects younger than 5 years of age and the percentage for subjects 5 through 17 years of age are shown in the following two tables.

Table 18. FLU-Q-TIV-(b)(4)-008 –Percentage of Subjects Less than 5 Years of Age with Individual Solicited Systemic Adverse Reactions during the Four Days Post-Vaccination (ATP Safety Cohort)

Type of Solicited Systemic Adverse Reaction	FluLaval (b)(4) N=293	Fluzone N=279
Any Drowsiness	21%	23%
Grade 3 Drowsiness*	1.4%	0.7%
Any Irritability	29%	31%
Grade 3 Irritability*	2.0%	1.4%
Any Loss of Appetite	18%	17%
Grade 3 Loss of Appetite*	2.4%	0.7%
Any Fever (≥38.0°)	5.1%	3.6%
Temperature ≥39.0°	1.0%	0.7%

*Grade 3 drowsiness and Grade 3 irritability were adverse reactions that interfered with daily activity; Grade 3 loss of appetite was eating less than usual
Source: BLA 125163/ SN 254, CSR Q-TIV-(b)(4)-008, Table 35, pages 96-98.

The percentage of subjects with individual solicited systemic adverse reactions was similar in both treatment groups. The percentage of subjects with Grade 3 adverse reactions was low (2% or less for each individual adverse reaction). Of note, there were no subjects in either group with fever of 40° or higher.

Table 19. FLU-Q-TIV-(b)(4)-008 –Percentage of Subjects 5 to 17 Years of Age with Individual Solicited Systemic Adverse Reactions during the Four Days Post-Vaccination (ATP Safety Cohort)

Type of Solicited Systemic Adverse Reaction	FluLaval (b)(4) N=750	Fluzone N=747
Any Muscle aches	27%	25%
Grade 3 Muscle aches*	0.8%	0.9%
Any Fatigue	18%	18%
Grade 3 Fatigue*	1.5%	1.3%
Any Headache	19%	17.5%
Grade 3 Headache*	0.8%	0.5%
Any Arthralgia	9.3%	11%
Grade 3 Arthralgia*	0.3%	0.3%
Any Shivering	6.0%	5.4%
Grade 3 Shivering*	0.3%	0.4%
Any Fever (≥38.0°)	2.5%	2.7%
Temperature ≥39.0°	0	0

*Grade 3 adverse reactions were those that interfered with daily activity
Source: BLA 125163/ SN 254, CSR Q-TIV-(b)(4)-008, Table 36, pages 99-102.

In subjects 5 through 17 years of age, muscle aches, fatigue, and headache were all reported in more than 10% of subjects in the FluLaval (b)(4) group. In the Fluzone group, arthralgia was also

reported in more than 10% of subjects. The percentage of subjects with fever was low, and no subjects had fever of 40° or higher. In subjects who received two doses of study vaccine, the percentage of subjects with each solicited systemic adverse reaction was lower after the second dose compared to the first for subjects in both treatment groups (data not shown).

Reviewer comment: In both age groups, the percentages of subjects with individual solicited adverse reactions were similar between the two study groups, Grade 3 adverse reactions were reported uncommonly, and in general, the percentage of subjects with individual solicited adverse reactions was lower after the second dose compared to the first. Although the type of individual solicited systemic adverse reactions were different in the two age groups, the percentage of subjects in the younger age group with individual solicited systemic adverse reactions was higher than in the older age group. However, the percentage of younger subjects with Grade 3 adverse reactions, including fever, was low. In addition, no febrile seizures were reported after vaccination in either treatment group.

Unsolicited adverse events were provided separately for two time periods of the study: the first time period was from Day 0 until 28 days after the final study vaccination and the second time period, called the extended safety study period, was from the time of the final study vaccination until Day 180. In the 28-day post-vaccination period, AEs were reported in 40% of FluLaval (b)(4) recipients and in 36.5% of Fluzone recipients. The unsolicited AEs reported in 2% or more of subjects during this post-vaccination time period are shown in the following table.

Table 20. FLU-Q-TIV-(b)(4)-008 – Percentage of Subjects with Unsolicited Adverse Events from Day 0 to 28 Days after the Last Study Vaccination (≥2% in Either Treatment Group) (ATP Safety Cohort)

	FluLaval (b)(4) Group N=1055	**Fluzone Group N=1061**
Cough	12%	11%
Pyrexia	5.9%	5.7%
Oropharyngeal pain	4.3%	3.7%
Rhinorrhea	4.3%	3.4%
Vomiting	3.6%	2.7%
Headache	2.8%	2.7%
Nasal congestion	2.7%	2.3%
Upper respiratory tract infection	2.5%	2.4%
Diarrhea	1.5%	2.5%
Nasopharyngitis	1.2%	2.1%

Source: BLA 125163/ SN 254, CSR Q-TIV-(b)(4)-008, Table 37, pages 103-124.

Most of the AEs reported in 2% or more of study subjects were from the Infections and Infestations system organ class. The most commonly reported unsolicited adverse events in both treatment groups were cough and pyrexia.

Grade 3 unsolicited adverse events in the 28-days post-vaccination were reported in 7.7% of FluLaval (b)(4) recipients and in 7.8% of Fluzone recipients. Grade 3 adverse events reported in more

than 1% of subjects in either study group were pyrexia (1.6% of FluLaval subjects and 1.1% of Fluzone subjects) and cough (0.9% of FluLaval subjects and 1.3% of Fluzone subjects).

Unsolicited AEs in the 28-days post-vaccination that were considered by the investigator to be vaccine related were reported in 6.2% of FluLaval (b)(4) subjects and in 5.4% of Fluzone subjects. These included 17 adverse events in the FluLaval (b)(4) group and 15 in the Fluzone group that were either additional reactions at the injection site such as hematoma, hemorrhage, or rash or prolonged injection site reactions such as pain and erythema. The only unsolicited AE that was considered by the investigator to be vaccine-related and that was reported in at least 1% of subjects was cough (1.4% of FluLaval (b)(4) recipients and 0.8% of Fluzone recipients).

Reviewer comment: The unsolicited adverse events reported in Study FLU-Q-TIV-(b)(4)-008 were reported in similar rates in the two treatment groups. Grade 3 AEs and AEs considered to be vaccine-related were reported at low rates, which were also similar in the two study groups. Overall, the unsolicited adverse events reported in the 28-days post-vaccination were consistent with common childhood illnesses.

Adverse events occurring in the six month follow-up period were reported in 36% of subjects in the FluLaval (b)(4) group and in 34% of subjects in the Fluzone group. The most commonly reported AEs during this time period were otitis media (6.5% of FluLaval (b)(4) recipients and 5.0% of Fluzone recipients), upper respiratory tract infection (5.7% of FluLaval (b)(4) recipients and 7.1% of Fluzone recipients), and pharyngitis (4.1% of FluLaval (b)(4) recipients and 3.4% of Fluzone recipients).

Medically attended adverse events during the entire study period were reported in 42% of subjects in the FluLaval (b)(4) group and in 41% of subjects in the Fluzone group. The most commonly reported medically attended AEs in both groups were otitis media and upper respiratory tract infections.

Reviewer comment: Unsolicited adverse events reported in the post-vaccination follow-up period and medically attended AEs reported during the entire study were observed in similar rates in both treatment groups. The types of adverse event and medically attended AEs were consistent with common childhood illnesses.

On examination of the WUNSOL dataset, the percentage of subjects reporting unsolicited adverse events during the entire study was 42% in the FluLaval (b)(4) group and 41% in the Fluzone group. The most commonly reported unsolicited adverse events during the entire study period were cough, upper respiratory tract infection, pyrexia, otitis media, and pharyngitis.

The unsolicited adverse event dataset was examined for preferred terms consistent with allergic reactions. Hypersensitivity was not reported in either treatment group. Urticaria was reported in two subjects within three days of study vaccination. One subjects in the FluLaval (b)(4) group reported urticaria over the trunk on the day of vaccination that was judged as moderate severity and lasted four days; a second subject reported urticarial on Day 3 that was also moderate in severity, lasted three days, and was judged to be vaccine-related. Neither required medical treatment. Eight subjects in the FluLaval (b)(4) group and one in the Fluzone group reported rashes in the two days post-vaccination. In the FluLaval group, two subjects had rashes at the injection site and five

subjects had rashes that were judged as vaccine related; but no rashes were severe, and all resolved within 11 days. Of note, there was one subject, a 13 year old female, in the FluLaval (b)(4) group who reported facial palsy Day 35. The facial palsy was judged as mild and not vaccine related.

Reviewer comment: The percentage of subjects with unsolicited AEs during the entire study period was similar in both study groups. On analysis of the WUNSOL dataset, more subjects in the FluLaval group reported rashes during the two days after vaccination compared to in the Fluzone group. However, the number of subjects with rashes was very small, most were mild, and all resolved within 11 days. Facial palsy has been reported after influenza vaccination and was reported in one subject in the FluLaval (b)(4) group. Although an association between the one case of facial palsy and FluLaval (b)(4) cannot be ruled out, it was a single case that was mild and resolved without sequelae.

6.1.12.3 Deaths

There were no deaths in this study.

6.1.12.4 Nonfatal Serious Adverse Events

A total of 24 serious adverse events (SAEs) were reported in 16 subjects: 10 subjects (<1%) with 15 SAEs in the FluLaval (b)(4) group and 6 subjects (<1%) with 9 SAEs in the Fluzone group.

Table 21. FLU-Q-TIV-(b)(4)-008 - Serious Adverse Events Reported in More than One Study Subject (ATP Safety Cohort)

SAE	FluLaval (b)(4) N=1055	Fluzone N=1061
Pneumonia	2	1
Herpangina	1	1
Oral candidiasis	1	1

Source: BLA 125163/ SN 254, CSR Q-TIV-(b)(4)-008, Table 39, pages 125-126.

Serious adverse events reported in one time only by treatment group were:

- FluLaval (b)(4) group: vomiting, abscess, appendicitis, cellulitis, H1N1 influenza, forearm fracture, convulsion, affective disorder, attention deficit disorder oppositional defiant disorder, and respiratory distress, and
- Fluzone group: bronchiolitis, gastroenteritis, diabetes mellitus, asthma, hypoxia, and sinus polyp.

Four subjects in the FluLaval (b)(4) group reported adverse events within 28 days of vaccination: one with forearm fracture, one with appendicitis, one with shoulder abscess, and one with H1N1 influenza, pneumonia, and respiratory distress. None of these were judged as vaccine-related. There were no SAEs in the Fluzone group in the 28 days after vaccination.

Two serious adverse events were judged to be related to study vaccination. These were:

- A 17 year old White female developed medically-refractory seizures 59 days after receiving FluLaval. She was treated with multiple medicines without resolution and seizure disorder was ongoing at the time the study ended.

- A 4 year old White male was diagnosed with insulin dependent diabetes mellitus 55 days after receiving Fluzone. He was hospitalized at the time of diagnosis, and the SAE was unresolved at the time the study ended.

Reviewer comment: The overall percentage of subjects with serious adverse events was similar in the two treatment groups. However, there were more SAEs reported in the time period after vaccination in the FluLaval group than in the Fluzone group. None of these SAEs were judged by the investigator as vaccine-related. In the opinion of this reviewer, the SAEs reported within 28 days of receipt of FluLaval (b)(4) are unlikely to be related to the study vaccine because of a lack of biologic plausibility. There was no increase in a single type of SAEs or in a single organ system in either group. The SAEs observed in this study were consistent with illnesses observed in pediatric patients. There were two serious adverse events that were judged by the investigator as related. In the opinion of this reviewer, it is difficult to determine if the two SAEs of diabetes and seizures were associated with study vaccine because of the lack of temporal relationship and the lack of other detailed information about these cases.

6.1.12.5 Adverse Events of Special Interest (AESI)

No adverse events of special interested were followed in this study.

6.1.12.6 Clinical Test Results

Not applicable

6.1.12.7 Dropouts and/or Discontinuations

The percentage of subjects who were excluded from the ATP safety cohort was small (<1%) and did not affect the study results. There were no premature study discontinuations due to adverse events.

6.2 Trial #2 – FLU-Q-QIV-006

Title: Efficacy Study of GSK Biologicals' Quadrivalent Influenza Vaccine, GSK2282512A, (FLU Q-QIV) When Administered in Children.

6.2.1 Objectives

The primary objective of the study was to evaluate the efficacy of Q-QIV in the prevention of RT-PCR positive influenza A and/or B disease presenting as influenza-like illness (ILI) compared to a non-influenza vaccine comparator (Havrix®, Hepatitis A vaccine) in children 3 through 8 years of age.

Secondary objectives of the study are described as follows:

1) To evaluate the efficacy of Q-QIV in the prevention of moderate to severe cases of influenza confirmed by RT-PCR, compared to Havrix;

   'Moderate to severe influenza' was defined as RT-PCR-confirmed ILI with fever > 39°C and/or one of the following symptoms:

physician-verified shortness of breath, pulmonary congestion, pneumonia, bronchiolitis, bronchitis, wheezing, croup, or acute otitis media, and/or physician-diagnosed serious extra-pulmonary complication of influenza, including myositis, encephalitis, seizure and/or myocarditis.

2) To evaluate the efficacy of Q-QIV (when compared to Havrix) in the prevention of culture-confirmed influenza A and/or B disease due to seasonal influenza strains antigenically matching the vaccine strains. If the preceding objective was achieved, then the study will evaluate the efficacy of Q-QIV in the prevention of culture-confirmed influenza A and/or B disease due to any seasonal influenza strain.

3) To describe the immunogenicity (geometric mean titer, seroconversion rate, seroconversion factor and seroprotection rate) of Q-QIV 28 days after completion of vaccination in a subset of subjects; and

4) To assess the reactogenicity/safety of Q-QIV in terms of solicited local and general symptoms during 7 days of follow up after each vaccination; unsolicited symptoms during 28 days of follow-up, serious AEs, medically attended adverse events and potential immune-mediated diseases throughout the entire study period.

Reviewer Comment: In the opinion of this reviewer, vaccine efficacy of FluLaval QIV in the prevention of culture-confirmed influenza A and/or B disease due to all strains and due to vaccine matched strains is an important secondary objective. The results for culture-confirmed influenza, therefore, will be included in the package insert for this product. Although the use of specific disease endpoints, including severe outcomes, may be useful in characterizing the vaccine efficacy of influenza vaccines, CBER did not agree with the GSK definition of 'moderate to severe influenza' because the definition aggregates conditions with widely varying degrees of severity. For example, the case definition of 'moderate to severe influenza' aggregates wheezing subjects with subjects diagnosed with encephalitis. The protocol did not provide a validated case definition for each of the influenza associated outcomes listed and important clinical outcomes (such as pneumonia) were not adjudicated, limiting the ability to characterize these findings inconsistent and accurate manner. Finally, the definition for 'moderate to severe influenza' includes signs and symptoms such as wheezing and shortness of

breath which have limited specificity. Please refer to Section 7.1.5 for additional discussion on this issue.

6.2.2 Design Overview

This trial was a Phase 3, observer blind, randomized, controlled, international and multi-center study of the efficacy of FluLaval QIV, administered intramuscularly in healthy children 3 through 8 years of age. A total of 5200 subjects were enrolled and randomized in a 1:1 ratio to receive either FluLaval QIV (n=2600) or Havrix® (Hepatitis A vaccine) (n=2600). Subjects received one or two doses of vaccine (either FluLaval QIV or Havrix) based on their influenza vaccination status or history of laboratory confirmed H1N1 infection. Bi-weekly, active ILI surveillance began 2 weeks after the day 0 visit until the final ILI follow up contact. All subjects received a diary card, an ILI booklet, and an ILI information sheet to facilitate passive surveillance at the day 0 visit. Subjects with an ILI episode had two additional clinic visits; nasal and throat swab specimens were collected as soon as possible (within 24 hours) of ILI symptom onset. A follow-up ILI contact occurred 15-22 days after ILI onset. Blood samples for immunogenicity testing were obtained at days 0 and 28 for all subjects with a history of vaccination with influenza vaccine, and days 0 and 56 for all subjects not previously vaccinated with influenza vaccine. All subjects were followed for approximately six months.

Reviewer Comment: The prospective, randomized study design offers controls for biases and allows for active monitoring of disease attack rates and careful tracking of vaccination status.

Havrix (Hepatitis A vaccine) was used as a control vaccine to benefit study subjects in the control arm, but it does not protect against influenza; therefore, FLU Q-QIV-006 provides information on the absolute vaccine efficacy of FluLaval QIV. For comparative safety and immunogenicity data on FluLaval QIV compared to a TIV product in children or adults, please refer to studies FLU Q-QIV-003 and FLU Q-QIV-007 (Sections 6.2 and 6.3).

6.2.3 Population

The study enrolled children 3 through 8 years of age, who were in stable health at the time of first vaccination.

A brief summary of the exclusion criteria follows:

1) Child in care, defined as 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

2) Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune modifying drugs within 6 months prior to the vaccine dose. Inhaled and topical steroids were allowed

3) History of Guillain-Barré syndrome within 6 weeks of receipt of prior inactivated influenza virus vaccine

4) Any known or suspected allergy to any constituent of influenza vaccines (including egg proteins); a history of anaphylactic-type reaction to consumption of eggs; or a history of severe adverse reaction to a previous influenza vaccine

5) Fever (temperature ≥ 38.0ºC or 100.4ºF by any method) at the time of enrollment

6) Acute disease (moderate or severe illness) at the time of enrollment

7) Any significant disorder of coagulation or treatment with Coumadin derivatives or heparin

8) Ongoing aspirin therapy (to avoid potential cases of Reye's syndrome)

9) Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination

10) Any other condition which, in the opinion of the Investigator, prevents the subject from participating in the study

Other eligibility criteria that may interfere with the immunogenicity evaluation of the vaccine (such as, but not limited to, subjects who received immunoglobulin and/or any blood products within the 3 months preceding the first dose of study) were also listed.

Reviewer Comment: The eligibility criteria define a healthy population in the 3 through 8 year age group. The external validity of the results of this vaccine efficacy study may be low for special populations excluded from the study, such as immunocompromised persons and pregnant women.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Subjects were randomized in a 1:1 ratio to receive either Havrix or FluLaval QIV.

Subjects randomized to receive FluLaval QIV received 0.5 mL of the investigational product (FluLaval QIV) intramuscularly (IM) in the deltoid muscle of the non-dominant arm. The vaccine lot numbers were: DFLHA586A and DFLHA642A .

Subjects randomized to the comparator vaccine received 0.5 mL of Havrix (lot number AHAVB353A) intramuscularly in the deltoid muscle of the non-dominant arm. Havrix is a sterile suspension of inactivated vaccine; each dose contained 720 ELISA Units of viral antigen (Hepatitis A strain HM175), adsorbed onto aluminum hydroxide (0.25 mg of aluminum).

Each dose of FluLaval QIV contained 15 µg of the following antigens (60 µg total):

- A/California/7/2009 (H1N1),
- A/Victoria/210/2009 (H3N2),
- B/Brisbane/60/2008 (Victoria lineage) and
- B/Florida/4/2006 (Yamagata lineage)

Both FluLaval QIV and Havrix were -----(b)(4)----- and were provided as --------(b)(4)--------, which may have contained -------(b)(4)--------.

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

---.

Subjects received one or two doses of vaccine depending on their priming status. Unprimed subjects randomized to receive FluLaval QIV or Havrix received two doses of vaccine at days 0 and 28. Primed subjects randomized to receive FluLaval QIV or Havrix received one dose of vaccine at day 0. Subjects randomized to receive Havrix, received a booster dose of Havrix at least 6 months after the first Havrix dose for control group subjects only.

Unprimed subjects were defined as follows:
Subjects aged 6 months through 8 years who have not received any influenza A (H1N1) 2009 monovalent vaccine in the past (or did not have laboratory confirmed H1N1 infection) OR who have not received any seasonal influenza vaccine in the past or received only one dose for the first time in the last influenza season.

Primed subjects were defined as follows:

Subjects aged 6 months through 8 years who have received at least one dose of an influenza A vaccine (H1N1) 2009 monovalent vaccine in the past (or had laboratory confirmed H1N1 infection) AND have received two doses of seasonal influenza vaccine separated by at least one month during last season or have received at least one dose prior to last season.

Reviewer Comment: The definitions of primed and unprimed were prespecified in the protocol and proposed by the Applicant. There is no regulatory definition for the terms "primed and unprimed."

6.2.5 Sites and Centers

This study was conducted at fifteen centers across Bangladesh, Dominican Republic, Honduras, Lebanon, Panama, Philippines, Thailand and Turkey

6.2.6 Surveillance/Monitoring

All subjects were followed using active and passive surveillance for approximately six months for evidence of ILI. ILI was defined as the presence of an oral or axillary temperature ≥ 37.8°C in the presence of at least one of the following symptoms on the same day: cough, sore throat, runny nose or nasal congestion.

Reviewer Comment: The definition for fever occurring with ILI differed from the Grade 1 definition of fever (temperature ≥ 38.0° C (100.4° F) - ≤ 38.5° C (101.3° F) *used in the protocol. Using this definition of fever, it is possible that cases of fever associated with RT-PCR positive ILI may be slightly overestimated in this study, although differences between groups will likely not be exaggerated due to the randomized study design.*

Passive ILI surveillance started on day 0; subjects' parents were instructed to contact the study center within 24 hours after subject became ill with symptoms consistent with ILI. Active surveillance of ILI began 2 weeks after day 0, parents and/or legally acceptable representatives were contacted by telephone every 2 weeks by study staff using a script to ask about the presence of unreported ILI or AEs.

Each ILI reported within seven days of onset was supposed to be evaluated. Nasal and throat swab specimens were to be collected, preferably within 24 hours. Parents or legally acceptable representatives were instructed to complete the ILI booklet for 15 days after ILI onset. The ILI booklet contained questions about the ILI episodes: what signs and symptoms are present (muscle aches, headache, sore throat, runny or stuffy nose, shortness of breath cough, vomiting, diarrhea, chills, and fatigue), if the ILI resulted in a medically attended visit or hospitalization, what medications were administered, if the subject missed school or daycare, and if a parent missed work to care for subject. The parent was also contacted 15-22 days after ILI onset to

confirm that the ILI booklet was completed and would be returned to the study site; information on symptoms, onset and end dates were also collected.

Nasal and throat swabs were collected from subjects for whom ILI was reported no more than seven days after onset. However, details regarding the ILI were still captured in the database. The ILI booklet was used for these subjects. Nasal and throat swabs were tested for influenza using RT-PCR. Cultures were performed on samples positive by RT-PCR.

Blood samples were collected from previously vaccinated subjects on day 0, day 28 and at the end of safety follow visit (ESFU visit, at least 6 months post-vaccination), and from unprimed subjects on day 0, 56 and at the ESFU visit. A subset of subjects (520 from the QIV group and 130 from the Havrix group) was to have their serum samples tested, while the other serum samples were stored. The immunogenicity subset was selected using systematic randomization from a random sample, every fifth subject in the Q-QIV group and every twentieth subject in the Havrix group (by vaccination order) was selected for the immunogenicity subset.

Solicited adverse reactions following vaccination from days 0 to 6 recorded by parent and/or legal guardian on diary card. The solicited local adverse reactions to be followed were pain, redness, and swelling at the injection site. Pain in children younger than 5 years of age was graded in intensity as follows:

- None (Grade 0)
- Mild (minor reaction to touch, Grade 1)
- Moderate (cries / protests on touch, Grade 2),
- Severe (cries when limb is moved / spontaneously painful, Grade 3)

Pain in children 5 years of age and older was graded as follows:

- None (Grade 0)
- Mild (present but not interfering with normal activity, Grade 1)
- Moderate (painful when limb is moved and interferes with daily activity, Grade 2)
- Severe (significant pain at rest, prevents normal activity, Grade 3).

The maximum intensity of redness and/or swelling was scored as follows:

- Grade 0 ($\leq$ 20 mm)
- Grade 1 ($\geq$ 20 - $\leq$ 50 mm)
- Grade 2 ($\geq$ 50 - $\leq$ 100 mm)
- Grade 3 ($>$ 100 mm)

The solicited systemic AEs were monitored in an age appropriate manner. Subjects younger than 5 years of age) were assessed for drowsiness, fever, irritability/fussiness, and loss of appetite. Subjects 5 years of age and older were assessed for fatigue/tiredness, fever, headache, joint pain, muscle aches (widespread or general), shivering (chills), and gastrointestinal

symptoms (nausea, vomiting, diarrhea, and/or abdominal pain). All solicited systemic AEs 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)
- Severe (prevents normal activity, Grade 3).

Fever was recorded as degrees in Centigrade or Fahrenheit and graded as follows:

- Grade 1: ≥ 38.0° C (100.4° F) - ≤ 38.5° C (101.3° F)
- Grade 2:≥ 38.5° C (101.3° F) - ≤ 39.0° C (102.2° F)
- Grade 3:≥ 39.0° C (102.2° F) - ≤ 40.0° C (104° F
- Grade 4: >40.0° C (104° F)

Unsolicited AEs that occurred from day 0 to day 27 were recorded by parent and/or legal guardian on the diary card. SAEs and MAEs were monitored throughout the trialTable 2 describes the schedule of study events for study FLU Q-QIV 006.

Table 22. Study FLU Q-QIV-006: Schedule ofEvents

Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Phone[b]
Trial Timelines (Days)	Day 0	Day 28	Day 56	At least 6 months	End of ILI Surveillance
Informed Consent	X				
Inclusion & Exclusion Criteria	X				
Medical History	X				
History- Directed Physical Examination	X				
Blood Sample (BS)†	X (BS1)	X	X (BS2)	X[a]	
Vaccination	X	X[a]			
Diary Cards (DC) Provided	X	X[a]			
Diary Cards Collected		X	X[a]		
Passive ILI surveillance	X	X	X		
Active ILI surveillance		X	X		
MAE, SAEs, pIMDs	X	X	X	X	X

[a]Unprimed subjects only
[b]A phone call was performed only if Visit 4 occurred prior to the end of the ILI surveillance period in the country.
Source: Adapted from sBLA 125163/SN 253; CSR, FLU Q-QIV-006, Tables 1-2, page 55-56

6.2.7 Endpoints and Criteria for Study Success

The primary (efficacy) endpoint for the study was:

1) First occurrence of RT-PCR positive influenza A and/or B disease from a nose and throat swab obtained concurrently with ILI.

The secondary endpoints of the study were:

1) First occurrence, during the ILI surveillance period of RT-PCR positive ILI with "moderate to severe influenza."

   Moderate to severe influenza was defined as follows:

   - Fever > 39°C and/or one of the following symptoms: physician verified shortness of breath, pulmonary congestion, pneumonia, bronchiolitis, bronchitis, wheezing, croup, or acute otitis media and/or one of the following,physician diagnosed serious extra pulmonary complication of influenza, including myositis, encephalitis, seizure and/or myocarditis

2) First occurrence of culture-confirmed influenza A and/or B disease due to influenza strains antigenically similar to those contained in the vaccine

3) First occurrence of culture-confirmed influenza A and/or B disease due to any influenza strains during the influenza surveillance period

4) The vaccine immunogenicity outcome was the serum hemagglutination inhibition (HI) antibody titer against each of the four vaccine influenza strains.

5) Occurrence, intensity and relationship to vaccination of solicited and unsolicited AEs.

6.2.8 Statistical Considerations & Statistical Analysis Plan

Study subjects were randomized in a 1:1 ratio to receive either FluLaval QIV or Havrix. Minimization factors included age subgroups (3 through 4 years and 5 through 8 years), history of influenza vaccination, priming status and country. Randomization was performed using the ---------(b)(4)----------.

Data was collected in an observer-blind manner. Study vaccines were administered by authorized medical personnel who did not participate in any of the study clinical evaluation.

It was calculated that 194 RT- PCR-confirmed ILI cases due to influenza A and B strains would be needed to demonstrate that the LL of the two-sided 95% CI for the VE is above 30% with 90% power. This calculation was based on the following assumptions: a true vaccine efficacy of 60% (based on 3 literature reviews); the influenza virus attack rate of 6% in the comparator group, and that 10% of subjects would be non-evaluable.

Based on this calculation, 5200 subjects (2600 per treatment group) were recruited to reach the required number of cases of RT-PCR positive ILI (194) due to influenza A and B strains. Although the study protocol allowed for a second year of the study if insufficient influenza cases were accrued during the first year of the study, the second year was not required because ≥ 194 RT-PCR positive influenza cases were attained in the first year of the study. For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements were not replaced. For a complete discussion of statistical considerations, please refer to the review provided by Dr. Sang Ahnn OBE/Division of Biostatistics/Vaccine Evaluation Branch.

6.2.9 Study Population and Disposition

The study began on December 9, 2010 and the last study visit was on January 9, 2012.

6.2.9.1 Populations Enrolled/Analyzed

The safety analysis was performed on the Total Vaccinated Cohort (TVC). Immunogenicity analyses were performed on the According To Protocol (ATP) Cohort for Immunogenicity (ATP-i). The efficacy analysis was performed on the ATP Cohort for Efficacy (ATP-e).

These cohorts were defined as follows:

- The TVC included all vaccinated subjects.
- The ATP-i included all subjects for whom assay results were available against at least 1 study vaccine antigen component after vaccination and who were within the maximum intervals allowed as defined in the protocol, and who did not present with a medical condition or product leading to exclusion.
- The ATP-e included all subjects who received the study vaccine per their treatment assignment, and had at least 1 follow up after the first vaccination, and who did not meet any criteria for elimination from the ATP analysis during the study.

6.2.9.1.1 Demographics

Demographic data for subjects enrolled in study FLU Q-QIV-006 are shown in Table 3.

Table 23. Study FLU Q-QIV-006: Summary of Demographic Characteristics (ATP Cohort for Efficacy)

		FLUQQIV N=2376		HAVRIX N=2389	
Characteristics	Parameters	Value (n)	%	Value (n)	%
Age (years) at Entry	Mean	5.4	-	5.4	-
Gender	Female	1158	48.7	1147	48.0
	Male	1218	51.3	1242	52.0
Race/Ethnicity	Asian	1410	59.3	1432	59.9
	White – Arabic/north African heritage	70	2.9	68	2.8
	White – Caucasian/European heritage	54	2.3	51	2.1
	African heritage/African American	2	0.1	6	0.3
	Other	840	35.4	832	34.8

Source: Adapted from sBLA 125163/ SN 253; CSR, FLU Q-QIV 006; page 133

The study enrolled roughly equal numbers of males and females. The majority of subjects enrolled in the study were Asian; White Caucasians comprised less than 5% of study subjects.

Reviewer Comment: No imbalances in randomization were identified. Although the study population differs from the racial ethnic composition of the U.S. population, no known differences in the safety and efficacy of inactivated influenza vaccination related to racial and/or ethnic factors exist.

6.2.9.1.2 Medical/Behavioral Characterization of the Enrolled Population

The majority of subjects (90%) had no history of influenza seasonal vaccination in the previous 3 seasons.

Reviewer Comment: The majority of subjects did not have a history or previous influenza vaccination. In this manner, the study population differed from the U.S. population for whom influenza vaccination is recommended annually. The baseline serostatus of subjects (shown in Table 10) suggests that a good percentage of subjects had been infected with influenza virus in the past. The exact manner by which baseline differences in immunity (acquired by natural influenza infection or by influenza vaccination) impact the safety and immunogenicity results of this study, and the applicability of these results to the U.S. population is uncertain.

6.2.9.1.3 Subject Disposition

Table 4 shows the number of subjects who were vaccinated, the number who completed the study and the number of subjects who were withdrawn from the study.

Table 24. Study FLU Q-QIV-006: Number of Subjects Withdrawn (TVC)

Disposition	FluLaval QIV	Havrix	Total
	N (%)	N (%)	N (%)
TVC	2584 (100)	2584 (100)	5168 (100)
Number of subjects completed	2481 (96)	2464 (95)	4945 (96)
Number of subjects withdrawn	103 (4)	120 (5)	223 (4)

Completed=number of subjects who completed last study visit
Source: Adapted from sBLA 125163/254; CSR FLU Q-QIV-006, Table 15, page 129

A small percentage (roughly 5%) of subjects withdrew from the study prematurely. The most common reason for withdrawal was withdrawal of consent not due to an AE (59% of subjects withdrawn). Only three subjects withdrew due to AEs; none of these subjects were withdrawn from the study by the Applicant. Protocol violations rarely occurred.

Reviewer Comment: Both arms of the study had similar attrition rates. The low overall study attrition rate did not raise concerns with respect to the introduction of bias or study conduct.

The number of subjects excluded from the TVC for the ATP cohort for efficacy and reasons for exclusion are shown in Table 5. For a detailed description of the cohorts of analysis, please see Section 6.1.10.

Table 25. Study FLU Q-QIV-006 – ATP Cohort for Efficacy with Reasons for Exclusion From TVC

Disposition	Total	Havrix	FluLaval QIV
	n (%)	n (%)	n (%)
Total Cohort	**5175**	**2587**	**2588**
Dose not administered, but subject number allocated	7	3	4
TVC	**5168 (100)**	**2584 (100)**	**2584 (100)**
Administration of medication/vaccine forbidden in the protocol	15 (<1)	5 (<1)	10 (<1)
Randomization code broken	2 (<1)	1 (<1)	1 (<1)
Study vaccine dose not administered ATP	137 (3)	72 (3)	65 (3)
Protocol violation (eligibility criteria)	3 (< 1)	0 (0)	3 (<1)
Noncompliance with vaccination schedule	232 (4)	123 (5)	109 (4)
Essential serologic data missing	3 (< 1)	1 (<1)	2 (<1)
Other	11 (<1)	6 (<1)	5 (<1)
ATP cohort for efficacy	**4765 (92)**	**2376 (92)**	**2389 (92)**

Source: Adapted from sBLA 125163/ SN 253; CSR QIV-006, Tables 15-16, pages 129-30
*Subjects with more than one deviation to the per-protocol are counted only once and are classified in the category of deviation listed first in this table.

The number of subjects excluded from the TVC for the primary analysis, the ATP cohort for efficacy, was 8%. The most common reason for exclusion was noncompliance with blood sampling/vaccination schedule.

Reviewer Comment: As the percentage of subjects excluded from the TVC in the ATP cohort for efficacy was greater than 5%, a second analysis based on the TVC was performed to complement the ATP analysis. No major differences in results were found (data not shown).

The number of subjects excluded from the TVC in the immunosubset for the ATP analysis of immunogenicity and reasons for exclusion are shown in Table 5.

Table 26. Study FLU Q-QIV-006 – ATP Cohort for Immunogenicity with Reasons for Exclusion from TVC

Disposition	Total	FluLaval QIV	Havrix
	n (%)	n (%)	n (%)
TVC in the Immunosubset	**707 (100)**	**544 (100)**	**163 (100)**
Administration of medication/vaccine forbidden in the protocol	1 (<1)	1 (<1)	0
Concomitant infection which may influence immune response	2 (<1)	2 (<1)	0
Study vaccine dose not administered ATP	*71 (10)*	*39 (7)*	*32 (20)*
Noncompliance with blood sampling/vaccination schedule	36 (5)	30 (6)	6 (4)
Essential serologic data missing	18 (3)	15 (3)	3 (2)
ATP cohort for immunogenicity	**579 (82)**	**457 (84)**	**122 (75)**

Source: Adapted from sBLA 125163/SN 253, CSR FLU Q-QIV-006, Table 18, Page 131.

A high percentage of subjects was excluded from the TVC to comprise the immunosubset; the most common reasons for exclusion was that the study vaccine dose was not administered according to protocol.

Reviewer Comment: Since the percentage of vaccinated subjects in the immunogenicity subset excluded was greater than 5%, a second analysis based on the TVC on the immunogenicity subset was performed to complement the ATP analysis. No major differences in results were found (data not shown).

6.2.10 Efficacy Analyses

6.2.10.1 Analyses of Primary Endpoint

The study demonstrated the efficacy of FluLaval QIV in the prevention of RT-PCR positive influenza A and/or B disease presenting as ILI when compared to a non-influenza vaccine in children 3 through 8 years of age. The influenza attack rates and vaccine efficacy of FluLaval QIV are shown in the following table.

Table 27. Study FLU Q-QIV-006 - FluLaval QIV: Influenza Attack Rates and Vaccine Efficacy against RT-PCR Positive Influenza in Children 3 through 8 Years of Age (ATP Cohort for Efficacy)

	N[a]	N[b]	Influenza Attack Rates % (n/N)	Vaccine Efficacy % (95% CI)
FLULAVAL QIV	2,379	58	2.4	55.4 (39.1, 67.3)
HAVRIX	2,398	128	5.3	–

CI = confidence interval; RT-PCR = reverse transcriptase polymerase chain reaction.
[a] ATP cohort for efficacy included subjects who met all eligibility criteria, were successfully contacted at least once post-vaccination, and complied with the protocol specified efficacy criteria.
[b]Number of influenza cases.
Source: Adapted from sBLA 125163/ SN 253, CSR, QIV-006, Table 28, page 139

The lower bound of the 95% CI was > 30%, which met the pre-specified success criterion for demonstration of efficacy.

6.2.10.2 Analyses of Secondary Endpoints

Vaccine efficacy of FluLaval QIV against culture-confirmed influenza A and/or B in children 3 through 8 years of age was demonstrated as shown in Table 8.

Table 28. FLU Q-QIV-006: Influenza Attack Rates and Vaccine Efficacy Against Culture- Confirmed Influenza in Children 3 through 8 Years of Age (ATP Cohort for Efficacy)[a]

	N[a]	**N[b]**	**Influenza Attack Rates % (n/N)**	**Vaccine Efficacy % (97.5% CI)**
Culture-Confirmed Influenza (Antigenically Matched Strains)				
FLULAVAL QIV	2,379	31	1.3	45.1 (9.3, 66.8)
HAVRIX	2,398	56	2.3	–
All Culture-Confirmed Influenza (Matched, Unmatched, and Untyped Strains)				
FLULAVAL QIV	2,379	50	2.1	55.9 (35.4, 69.9)
HAVRIX	2,398	112	4.7	–

CI = CI; RT-PCR = reverse transcriptase polymerase chain reaction.
[a]ATP cohort for efficacy included subjects who met all eligibility criteria, were successfully contacted at least once post-vaccination, and complied with the protocol specified efficacy criteria.
[b]Number of influenza cases.
Source: Adapted from sBLA 125163/ SN 253, CSR, QIV-006, Tables 30-31, Pages 141-2.

Vaccine efficacy against culture-confirmed influenza due to antigenically matched strains was lower than vaccine efficacy against culture-confirmed influenza due to matched, unmatched and untyped strains. Of 162 culture-confirmed influenza cases, 108 (67%) were antigenically typed (87 matched; 21 unmatched); 54 (33%) could not be antigenically typed [but were typed by RT-PCR and nucleic acid sequence analysis: 5 cases A (H1N1) (5 with Havrix), 47 cases A (H3N2) (10 with FluLaval QIV; 37 with Havrix), and 2 cases B Victoria (2 with Havrix].

Reviewer Comment: Typically, influenza vaccines have higher vaccine efficacy against matched influenza vaccine strains. However, in this study, vaccine efficacy against culture confirmed influenza due to antigenically matched strains was lower than vaccine efficacy calculated using other methods (RT-PCR positive influenza and culture-confirmed influenza due to any influenza strain). The decreased efficacy noted in this analysis may have been due to the difficulties in typing influenza viruses. The methods used for antigenic typing by culture were validated, and found to be suitable for intended use by CBER reviewers. However, influenza viruses have a high mutation rate resulting in the emergence of new strains that differ to varying degrees from the strains used in the seasonal vaccines. This provides challenges in typing viruses. Whether the study has enough strength statistically depends on how much the viruses mutate, how well matched the vaccine is to circulating strains and how severe the season is. As the study was not powered to evaluate the prevention of culture-confirmed influenza due to antigenically matched strains, the clinical significance of this finding is unknown.

The Applicant defined the term 'moderate to severe influenza,' a collection of thirteen adverse outcomes of varying severity, associated with ILI.

Reviewer Comment: CBER did not agree with the definition proposed by the Applicant for 'moderate to severe influenza.' Please refer to Section 6.1.1 for further discussion regarding use of the term 'moderate to severe' influenza, as defined by the Applicant.

The incidence of these influenza associated adverse outcomes (TVC) is shown in Table 9.

Table 29. Study FLU Q-QIV-006: Incidence of Influenza-Associated Adverse Outcomes in Subjects with RT-PCR-Positive Influenza Like Illness (ILI) from 14 days Post-Vaccination Through the End of ILI Surveillance (TVC)

Event	Q-QIV N=2584 N (%)	Havrix N=2584 n (%)
Fever (>39ºC)	15 (0.6)	50 (2)
Shortness of breath	0	5 (0.2)
Pneumonia	0	3 (0.1)
Bronchitis	1 (0)	1 (0)
Wheezing	1 (0)	1 (0)
Acute Otitis Media	0	1 (0)
Pulmonary Congestion	0	1 (0)
Seizure	0	0
Bronchiolitis	0	0
Croup	0	0
Encephalitis	0	0
Myocarditis	0	0
Myositis	0	0

Source: Adapted from sBLA 125163/ SN 253, CSR FLU Q-QIV-006, Table 35, page 163

As shown in Table 9, fever > 39ºC was the only influenza associated adverse outcome observed in > 1% of subjects in the Havrix arm. The risk reduction of fever >102.2°F/39.0°C associated with RT-PCR-positive influenza was 71.0% (95% CI: 44.8, 84.8) based on the ATP cohort for efficacy [FluLaval QIV (n = 12/2,379); Havrix (n = 41/2,398)]. The other pre-specified adverse outcomes had too few cases to calculate a risk reduction.

Reviewer Comment: Few of the influenza associated adverse outcomes, except for fever, were observed in this study. In the opinion of this reviewer, fever is a frequent clinical manifestation of influenza disease and does not constitute a moderate or severe manifestation of influenza. Pneumonia, however, is commonly considered a severe outcome of influenza disease. As shown in the table above, a slightly higher number of cases of pneumonia appeared to occur in the FluLaval QIV group than the Havrix group. However, this study was not powered to evaluate risk reduction of pneumonia by FluLaval QIV; these findings neither support nor refute the efficacy of FluLaval QIV in the prevention of pneumonia.

Serum HI antibody levels were measured as a secondary endpoint. Antibody levels were assessed using the percentages of subjects with post-vaccination HI titers ≥ 1:40 and seroconversion rates. The percentage of subjects vaccinated with FluLaval QIV who had post-vaccination HI titers ≥ 1:40 is shown in Table 10 for each influenza strain.

Table 30. Study FLU Q-QIV-006: Percentage of Subjects with HI titers ≥1:40

(ATP Cohort for Immunogenicity)

		FluLaval QIV Arm		**Havrix Arm**	
Influenza Strain	N[a]	Pre-Vaccination (95% CI)	Post-Vaccination[b] (95% CI)	Pre-Vaccination (95% CI)	Post-Vaccination[b] (95% CI)
A/H1N1	457	33.0 (28.7, 37.6)	98.7 (97.2, 99.5)	32 (23, 41)	32 (24, 41)
A/H3N2	457	44.9 (40.2, 49.5)	97.4 (95.5, 98.6)	54 (44, 63)	52 (42, 61)
B/Victoria	457	27.8 (23.7, 32.1)	96.9 (94.9, 98.3)	30 (22, 39)	32 (24, 41)
B/Yamagata	457	34.8 (30.4, 39.4)	98.9 (97.5, 99.6)	39 (30, 48)	39 (30, 48)

[a]N=number of subjects with available results;
[b]Antibody titers were measured 28 days after the last study vaccination Source: Adapted from sBLA 125163/ SN 253; CSR, QIV-006, Table 68, page 207

Table 31. Study FLU Q-QIV-006: Seroconversion Rates (SCR)[a] for HI titers 28 Days Post-Vaccination (ATP Cohort for Immunogenicity)

Influenza Strain	N[b]	FluLaval QIV SCR % (95% CI)	Havrix SCR % (95% CI)
A/H1N1	457	96 (94, 98)	1 (0, 5)
A/H3N2	457	84 (81, 88)	2 (0, 6)
B/Victoria	457	93 (90, 95)	3 (1, 7)
B/Yamagata	457	95 (93, 97)	1 (0, 5)

[a] Seroconversion rate was defined for initially seronegative subjects as HI titer ≥ 1:40 post-vaccination and for initially seropositive subjects as four fold or greater rise in antibody titer post-vaccination.
[b] Number of subjects with pre and post vaccination results available.
Source: Adapted from sBLA 125163/ SN 253; CSR, QIV-006, Table 67, page 207

The percentage of subjects with post-vaccination HI titer ≥ 1:40 was greater than 95% for all four strains and the seroconversion rate was greater than 80% for all four strains.

Reviewer Comment: HI titers ≥ 1:40 and seroconversion rates both appear to overestimate actual vaccine efficacy which was much lower, and casts doubt on the use of 1:40 as a seroprotective tite

6.2.10.3 Subpopulation Analyses

Vaccine efficacy against RT-PCR-confirmed influenza A and/or B disease presenting as ILI in subjects 3 through 4 years of age was lower than vaccine efficacy in subjects 5 through 8 years of age, as shown in the following table.

Table 32. Study FLU Q-QIV-006: Vaccine Efficacy for Prevention of RT-PCR Positive ILI by Age Group

Age Group	VE	95% CI
3 through 4 years of age	35.3%	(-1.3;58.6)
5 through 8 years of age	67.7%	(49.7;79.2)

*VE was based on Cox regression, adjusted for region, and priming status as covariates.
Source: Statistical Review by Dr. Sang Ahnn, OBE/Division of Biostatistics/Vaccine Evaluation Branch

Immunogenicity data by age subgroups did not correlate well with this finding. As shown in Tables 13 and 14, the HI titers as measured by seroconversion rates and percentages of subjects with post-vaccination HI titers ≥ 1:40 were similar in the two age cohorts.

Table 33. Study FLU Q-QIV-006: Percentages of Subjects With HI Titers ≥ 1:40 at Day 28 Post-Vaccination by Age (ATP Cohort for Immunogenicity)

	3 through 4 years of age		5 through 8 years of age	
Influenza Strain	Pre-Vaccination (95% CI)	Post-Vaccination (95% CI)	Pre-Vaccination (95% CI)	Post-Vaccination (95% CI)
A/H1N1	40 (32, 48)	98 (94, 99)	30 (24, 35)	99 (98, 100)
A/H3N2	48 (40, 56)	94 (89, 97)	43 (38, 49)	99 (98, 100)
B/Victoria	24 (17, 31)	96 (92, 99)	30 (25, 36)	97 (95, 99)
B/Yamagata	22 (15, 29)	98 (95, 100)	42 (36, 48)	99 (98, 100)

CI= Confidence Interval; ATP = According To Protocol; HI = hemagglutinin inhibition
Source: Adapted from sBLA 125163/ SN 253; CSR, Q-QIV-006, Table 73, page 216

Table 34. Study FLU Q-QIV-006: Seroconversion Rate for HI Titers 28 Days after Last Vaccination by Age (ATP Cohort for Immunogenicity)

Influenza Strain	3 through 4 years of age SCR % (95% CI)	5 through 8 years of age SCR % (95% CI)
A/H1N1	94 (90, 97)	97 (94, 98)
A/H3N2	86 (80, 91)	83 (79, 88)
B/Victoria	93 (88, 97)	93 (89, 96)
B/Yamagata	98 (94, 99)	94 (91, 96)

[a]N=number of subjects with available results;
[b]n=number of subjects with HI titers ≥ 40 1/DIL (3 through 4 years of age)
[c]n=number of subjects with HI titers ≥ 40 1/DIL (5 through 8 years of age)
Source: Adapted from sBLA 125163/ SN 253; CSR, QIV-006, Table 72, page 215

Reviewer Comment: As the study lacked statistical power to evaluate efficacy within age subgroups, the clinical significance of these results is unknown. The immunogenicity data by age subgroup did not correlate well with the finding of decreased vaccine efficacy in the younger age group. This information will be included in the FluLaval QIV package insert with appropriate caveats about its interpretation.

6.2.10.4 Vaccine Efficacy by Gender, Race or County

Subgroup analyses of efficacy by gender, race, or country (Bangladesh, Dominican Republic, Honduras, Lebanon, Panama, Philippines, Thailand, and Turkey) did not show any substantial differences in vaccine efficacy of FluLaval QIV by genders, race groups, or countries (data not shown).

6.2.11 Safety Analyses

6.2.11.1 Methods

The safety analysis was performed on the TVC.

6.2.11.2 Overview of Adverse Events

Subjects reported local adverse reactions more frequently than systemic adverse reactions.

The percentages of subjects with solicited local adverse reactions occurring within 7 days of vaccination are shown in Table 15.

Table 35. Study FLU Q-QIV-006: Percentages of Subjects with Solicited Local Adverse Reactions Within 7 Days[a] of First Vaccination in Children 3 through 8 Years of Age (TVC)

Local Adverse Reaction	FLULAVAL QIV % N=2546	HAVRIX % N=2551
Pain	39	28
Grade 3 Pain	0.9	0.7
Swelling	1	0.3
Grade 3 Swelling	0	0
Redness	0.4	0.2
Grade 3 Redness	0	0

Source: Adapted from sBLA 125163/ SN 253, CSR FLU Q-QIV-006; Table 102; Page 247.

Pain was the most commonly occurring adverse reaction, reported in 39% of FluLaval QIV recipients compared to 28% of Havrix recipients. The occurrence of grade 3 pain was rare. Redness and swelling occurred in ≤ 1% of subjects; no grade 3 redness or swelling occurred.

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

Table 36. Study FLU Q-QIV-006: Percentage of Subjects with Solicited Systemic Adverse Reactions Within 7 Days[a] of First Vaccination in Children 3 through 8 Years of Age[b](TVC)

	FluLaval QIV %	Havrix %
	3 through 4 Years of Age	
	N = 898	N = 895
Loss of appetite	9	8
Irritability	8	8
Drowsiness	8	7
Fever ≥100.4°F (38.0°C)	4	4
	5 through 8 Years of Age	
	N = 1,648	N = 1,654
Muscle aches	12	10
Headache	11	11
Fatigue	8	7
Arthralgia	6	5
Gastrointestinal symptoms[c]	6	6
Shivering	3	3
Fever ≥100.4°F (38.0°C)	3	3

TVC=Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were available.
[a]7 days included day of vaccination and the subsequent 6 days.
[b] Solicited systemic adverse reactions were followed in an age-appropriate manner for younger children.
[c]Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.
Source: Adapted from sBLA 125163/ SN 253; CSR QIV-006; Tables 102-104; pages 247-251

The incidence of fever ≥39°C within 7 days of vaccination in subjects below 5 years of age, was 1.3% in the FluLaval QIV group and 1.1 % in the Havrix group. (overall per dose). No reports of febrile convulsion occurred in subjects assigned to the FluLaval QIV group; one case of febrile convulsion occurred in the Havrix group.

The frequency of unsolicited AEs was similar in both groups (33% for both FluLaval QIV and Havrix). Nasopharyngitis, which was the most commonly reported unsolicited AE in both study arms. Other unsolicited AEs reported by ≥1% of subjects in the FluLaval QIV group were diarrhea, pyrexia, gastroenteritis, upper respiratory tract infection, varicella, cough, and rhinorrhea. The types of unsolicited AEs reported by ≥1% of Havrix recipients were similar. The percentages of grade 3 unsolicited AEs occurring within the 28 day period post-vaccination (TVC) were 1% in the FluLaval QIV arm, compared to 0.8% in the Havrix arm. Unsolicited adverse reactions (i.e., AEs judged by the investigator to be related to vaccination) occurring within 28 days were reported by 1.2% (30/2584) of subjects in the FluLaval QIV arm and 1.4% (37/2584) of subjects in the Havrix arm. Serious adverse events occurring within 28 days of any

vaccination were reported in 0.7% of subjects who received FluLavla QIV, and in 0.2% of subjects who received Havrix.

Reviewer Comment: The percentage of subjects with any unsolicited AEs occurring within 28 days of vaccination was similar across study arms. In addition, the types of unsolicited AEs observed were consistent with common childhood symptoms and illnesses. These data do not raise a safety concern associated with FluLaval QIV. SAEs rarely occurred within 28 days of vaccination

6.2.11.3 Deaths

There were two deaths in this study; the study investigators determined that these deaths were not related to the study investigation.

- A 3 year old female drowned 128 days after receiving second dose of FluLaval QIV.
- A 3 year old male drowned 7 days after receiving first dose of Havrix.

Reviewer Comment: The narratives for these deaths were reviewed. The investigator's conclusion that the deaths were not related to study vaccine appears reasonable.

6.2.11.4 Nonfatal Serious Adverse Events

An analysis of nonfatal SAEs occurring during the entire study period and occurring within 28 days post-vaccination was performed. Nonfatal SAEs attributed to the vaccine by the study investigator were also evaluated.

During the entire study period, nonfatal SAEs occurred infrequently in both FluLaval QIV and Havrix recipients (1.4-0.9%, respectively). During the 28 days post-vaccination, < 1% of subjects reported nonfatal SAEs in each study group. A slightly higher percentage of nonfatal SAEs were reported by subjects assigned to the FluLaval QIV group (0.7%) than the Havrix group (0.3%), however. The most frequent nonfatal SAE occurring within 28 days of vaccination was pneumonia or bronchopneumonia.

Table 37. Study FLU Q-QIV-006: Number of Nonfatal Serious Adverse Events Occurring Within 28 Days of Vaccination by Study Group (TVC)

Preferred Term	FluLaval QIV N=2584	Havrix N=2584
Pneumonia or bronchopneumonia	4	1
Animal bites	3	0
Gastroenteritis or infectious diarrhea	2	1
Bronchitis	2	0
Amebiasis	1	1
Bronchiolitis	1	0
Croup	1	0
Respiratory distress	1	0
Influenza like illness	1	0
Appendicitis	1	0
Herpes zoster	1	0
Urinary tract infection	1	0
Convulsion	1	0
Joint injury	1	0
Dengue fever	0	1
Visceral leishmaniasis	0	1
Tonsillitis	0	1
Optic nerve glioma	0	1
Total	20 (0.7)	7 (0.3)

QIV=quadrivalent
Source: Adapted from sBLA 125163/ SN 253, Table 138, page 308

Only one nonfatal SAE considered by study investigators to be possibly related to vaccination occurred in the FluLaval QIV group. A 7 year old male from Panama was hospitalized on the day of his second vaccination with FluLaval QIV, with symptoms of cough, vomiting, shortness of breath and fever (39.5°C). His white blood cell count 1 day after admission was mildly elevated. He received supportive care, including treatment with antihistamine for possible allergic reaction. The symptoms resolved 10 days later.

Reviewer Comment: The timing of the nonfatal SAE in the 7 year old subject described raises the possibility that the subject experienced an allergic reaction to the vaccine. Although allergic reactions including anaphylaxis are a known adverse reaction to inactivated influenza vaccines, the high fever in this patient makes alternative etiologies (such as infection due to a bacterial or viral etiology) appear more likely.

As an aside, an analysis of the number of subjects with hypersensitivity within two days of vaccination showed that 2 cases of hypersensitivity occurred, one in each treatment group (data not shown).

Overall, the low percentage of nonfatal SAEs reported in the FluLaval QIV supports the safety of this product. The diagnoses of nonfatal SAEs reported in two or more subjects in the FluLaval QIV arm, reflect illnesses commonly observed in the population studied.

6.2.11.5 Potential Immune Mediated Diseases (pIMDs)

No pIMDs occurred in subjects assigned to the FluLaval QIV arm. The study investigators diagnosed one pIMD, glomerulonephritis, in a recipient of Havrix; the diagnosis was not considered related to vaccination with Havrix.

Reviewer Comment: The study did not detect an increased association between pIMDs and FluLaval QIV.

6.2.11.6 Clinical Test Results

There were no clinical laboratory evaluations in this trial.

6.2.11.7 Dropouts and/or Discontinuations

No dropouts and/or discontinuations of study participants appear to have occurred due to vaccine-related issues. Two subjects withdrew from the study due to death not related to FluLaval QIV. One non serious AE led to premature discontinuation of a subject assigned to the Havrix group.

6.2.11.8 Conclusions

- The absolute vaccine efficacy in preventing RT-PCR positive influenza A and/or B disease presenting as ILI was 55%, (LL of 95% CI: 39%). The absolute vaccine efficacy in preventing culture confirmed influenza A and/or B disease presenting as ILI was comparable.

- However, vaccine efficacy against culture confirmed influenza disease due to vaccine matched strains was lower (point estimate 45%; LL of 95% CI was 9%). This finding may have been due to difficulty in typing influenza strains.

- In an exploratory analysis by age, vaccine efficacy against RT-PCR-positive influenza A and/or B disease presenting as ILI in subjects 3 through 4 years of age was lower (35%; 95% CI: -1.3, 59) than in subjects 5 through 8 years of age (67.7% ; 95% CI: 49.7, 79.2). As the study lacked statistical power to evaluate efficacy within age subgroups, the clinical significance of these results is unknown.

- No safety concerns associated with FluLaval QIV were identified. Although FluLaval QIV causes increased injection site pain, these reactions were mild. No imbalances in the frequency or severity of solicited or unsolicited AEs or group of AEs were observed. An increase in SAEs or uncommon conditions was not observed.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

There is only one indication, which is for the active immunization against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. FluLaval is approved for use in persons 3 years of age and older.

7.1.1 Methods of Integration

The applicant submitted the results of a single study of the trivalent formulation of FluLaval to support the safety and effectiveness of FluLaval in pediatric subjects. The results of a second study were submitted to support the traditional approval of FluLaval. Although both studies were conducted in children, one was an immunogenicity and safety study and the other was a clinical endpoint study. The study objectives and study design, including endpoints, were too different to allow for integration.

7.1.2 Demographics and Baseline Characteristics

Please see discussion of Study FLU-Q-TIV-(b)(4)-008 in Section 6.1.

7.1.3 Subject Disposition

Please see discussion of Study FLU-Q-TIV-(b)(4)-008 in Section 6.1.

7.1.4 Analysis of Primary Endpoint(s)

Due to differences in study design and study populations, the pooling of data from individual studies was determined to be of limited value. Please see the reviews of the individual studies in Section 6.

7.1.5 Analysis of Secondary Endpoint(s)

Please see the reviews of the individual studies in Section 6.

7.1.6 Other Endpoints

Please see the reviews of the individual studies in Section 6.

7.1.7 Subpopulations

Please see Section 6.1 for an analysis of immunogenicity by age subgroup. The percentage of subjects who were female was 47%. The result for the primary endpoint by gender is shown in the following tables.

Table 38. FLU Q-TIV-(b)(4)-008 – Results for Non-Inferiority Analysis Comparing FluLaval (b)(4) to Fluzone in Male and Female Subjects using GMT Ratios by Gender (ATP Immunogenicity Cohort)

Influenza Strain	Males (N=1046)		Females (N=919)	
	Value	UL 95% CI*	Value	UL 95% CI*
A/H1N1	0.99	1.13	1.07	1.22
A/H3N2	0.97	1.09	1.14	1.28
B	1.0	1.14	0.87	0.99

*UL 95% CI = upper limit of the 95% confidence interval
Source: BLA 125163/ SN 254, Sequence 0124, Tables 3, 5, pages 7-8.

The criteria for demonstration of non-inferiority using GMT ratios were an upper limit of the 95% CI for the GMT ratio of less than 1.5. This endpoint was met for males and for females for all three influenza strains.

Table 39. FLU Q-TIV-(b)(4)-008 – Results for Non-Inferiority Analysis Comparing FluLaval (b)(4) to Fluzone in Male and Female Subjects using Difference in Seroconversion Rates by Gender (ATP Immunogenicity Cohort)

Influenza Strain	Males (N=1046)		Females (N=919)	
	%	UL 95% CI*	%	UL 95% CI*
A/H1N1	-1.90%	4.10%	-1.06%	5.23%
A/H3N2	-6.01%	-0.32%	2.49%	8.54%
B	0.19%	5.18%	-5.29%	-0.25%

*UL 95% CI = upper limit of the 95% confidence interval
Source: BLA 125163/ SN 254, Sequence 0124, Tables 4, 6, pages 7-8.

The criteria for demonstration of non-inferiority using difference in seroconversion rates were an upper limit of the 95% CI for the GMT ratio of less than 10. This endpoint was met for males and for females for all three influenza strains.

The majority of the study population was White Caucasian (77%); therefore subgroup analysis by race was not performed. However, an analysis for Hispanic/Latino compared to non-Hispanic or Latino was performed and is shown in the following tables.

Table 40. FLU Q-TIV-(b)(4)-008 – Results for Non-Inferiority Analysis Comparing FluLaval (b)(4) to Fluzone using GMT Ratios by Ethnicity (ATP Immunogenicity Cohort)

Influenza Strain	Hispanic/Latino (N=463)		Non- Hispanic/Latino (N=1502)	
	Value	UL 95% CI*	Value	UL 95% CI*
A/H1N1	0.95	1.14	1.06	1.17
A/H3N2	0.98	1.15	1.07	1.18
B	0.89	1.09	0.94	1.05

*UL 95% CI = upper limit of the 95% confidence interval
Source: BLA 125163/ SN 254, Sequence 0124, Tables 7, 9, pages 9-10.

The criteria for demonstration of non-inferiority using GMT ratios were met for Hispanic/Latino ethnicity and for non-Hispanic/Latino ethnicity for all three influenza strains.

Table 41. FLU Q-TIV-(b)(4)-008 – Results for Non-Inferiority Analysis Comparing FluLaval (b)(4) to Fluzone using Difference in Seroconversion Rates by Ethnicity (ATP Immunogenicity Cohort)

Influenza Strain	Hispanic/Latino (N=463)		Non- Hispanic/Latino (N=1502)	
	%	UL 95% CI*	%	UL 95% CI*
A/H1N1	-3.53%	5.43%	-1.00%	3.97%
A/H3N2	-4.25%	4.27%	-1.33%	3.42%
B	-9.73%	4.63%	-2.37%	1.73%

*UL 95% CI = upper limit of the 95% confidence interval
Source: BLA 125163/ SN 254, Sequence 0124, Tables 8, 10, pages 9-10.

The criteria for demonstration of non-inferiority using the difference in seroconversion rate were met for Hispanic/Latino ethnicity and for non-Hispanic/Latino ethnicity for all three influenza strains.

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. Duration of immunogenicity/efficacy were not evaluated in the studies submitted to this supplement.

7.1.9 Product-Product Interactions

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

7.1.10 Additional Efficacy Issues/Analyses

There are no additional efficacy issues.

7.1.11 Efficacy Conclusions

The effectiveness of FluLaval is supported by the results from Study FLU-Q-TIV-(b)(4)-008. In this Phase III, randomized, observer-blind study, 2116 children from 3 through 17 years of age were vaccinated with FluLaval (b)(4) (N=1055) or with Fluzone, a U.S.-licensed seasonal influenza vaccine. The immunogenicity response to influenza antigens met the pre-defined primary endpoint. The antibody response to FluLaval (b)(4) was non-inferior to the antibody response to Fluzone using the analysis of GMT ratios and the difference in seroconversion rates. In addition, the efficacy of FluLaval (b)(4) can be inferred from the results for FluLaval Quadrivalent in the clinical endpoint study, FLU Q-QIV-006. The study results for FluLaval Quadrivalent are relevant to FluLaval because the two vaccines are manufactured using the same processes and have overlapping components. Vaccine efficacy of FluLaval Quadrivalent was 55.4%. In conclusion, the results from these two studies support the effectiveness of FluLaval in persons 3 through 17 years of age.

8. INTEGRATED OVERVIEW OF SAFETY

The supplemental BLA included the results of an immunogenicity and safety study in children 3 through 17 years of age. The results of a clinical endpoint study of FluLaval Quadrivalent were also included for support of the traditional approval of FluLaval. The safety results of these studies cannot be combined because of 1) different length of time that solicited adverse reactions were followed (4 days compared to 7 days), 2) influenza comparator and non-influenza comparator designs, and 3) the presence of a fourth influenza antigen in FluLaval Quadrivalent may have affected the safety results.

Only the safety results of Study FLU-Q-TIV-008 will be included in the package insert for FluLaval (trivalent formulation). Therefore, only those results are discussed in this section.

8.1 Safety Assessment Methods

Both studies in this supplement assessed safety by collection of information on solicited adverse events; unsolicited adverse events for 28 days post-vaccination; and collection of medically-attended adverse events, adverse events leading to premature study discontinuation, serious adverse events, and deaths for the entire study period. The methods of assessment were appropriate for the evaluation of the safety of FluLaval in pediatric patients.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

In Study FLU-Q-TIV-(b)(4)-008, the total vaccinated cohort and included 1055 subjects who received at least one dose of FluLaval. Subjects received one 0.5 mL dose administered intramuscularly. This is the dose and the method of administration that will be described in the package insert.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

In the Study FLU-Q-TIV-(b)(4)-008, 1055 subjects received FluLaval; of these 298 were 3 to 4 years of age, 390 were 5 to 8 years of age, and 367 were 9 to 17 years of age. The percentage of females was 47.4%. The majority (78.3%) of subjects were White / Caucasian. The study population is similar to the population of the U.S. (www.census.gov).

8.2.3 Categorization of Adverse Events

Adverse events were reported in the Clinical Study Reports as Preferred Terms using the MedDRA dictionary. The actual 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

Not applicable

8.4 Safety Results

Please see the safety results in Section 6.1.12.

8.4.1 Deaths

There were no deaths in the study.

8.4.2 Nonfatal Serious Adverse Events

Serious adverse events were reported in 10 subjects (<1%) who received FluLaval and in 6 subjects (<1%) who received Fluzone. Four subjects in the FluLaval (b)(4) group reported adverse events within 28 days of vaccination: one with forearm fracture, one with appendicitis, one with shoulder abscess, and one with H1N1 influenza, pneumonia, and respiratory distress. None of these were judged as vaccine-related. There were no SAEs in the Fluzone group in the 28 days after vaccination. Two serious adverse events were judged to be related to study vaccination; one in each treatment group. A 17 year old female who received FluLaval developed a seizure disorder on Day 59 and a 4 year old male who received Fluzone was diagnosed with insulin-dependent diabetes mellitus on Day 55.

Although there was an imbalance in the number of subjects with serious adverse events in the 28 days post-vaccination, none of these adverse events were judged as vaccine

related. In the opinion of this reviewer, none of the SAEs in this study appear to be definitively related to study vaccine.

8.4.3 Study Dropouts/Discontinuations

There were no premature study discontinuations due to adverse events.

8.4.4 Common Adverse Events

The most commonly reported adverse event or adverse reaction in the study of FluLaval (b)(4) was pain at the injection site, which was reported in 59% of subjects. Adverse events or reactions reported in 10% or more subjects were drowsiness (21%), irritability (29%), and loss of appetite (18%) in children younger than 5 years of age, and muscle aches (27%), headache (19%), and fatigue (18%) in subjects 5 years of age and older. The only unsolicited AE reported in at least 10% of subjects was cough, which was reported in 10% of subjects who received FluLaval. The unsolicited adverse events reported were consistent with illnesses common in pediatric populations.

8.4.5 Clinical Test Results

There were no clinical tests performed.

8.4.6 Systemic Adverse Events

See Section 6.1.12 for a complete discussion of systemic adverse events.

8.4.7 Local Reactogenicity

See Section 6.1.12 for a full discussion of local adverse reactions.

8.4.8 Adverse Events of Special Interest

Information of adverse events of special interest was not collected.

8.5 Additional Safety Evaluations

Not applicable

8.5.1 Dose Dependency for Adverse Events

Unprimed pediatric subjects from 3 to 8 years of age received two study vaccinations administered 28 days apart. In general, local and systemic solicited adverse reactions were reported after the first vaccine compared to the second vaccine. However, redness at the injection site was reported more frequently after the second dose of FluLaval (b)(4) than the first. The reason for this is unclear. Please see Section 6.1.12 for a complete discussion.

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

Solicited local adverse reactions are analyzed by age subgroup in the following table.

Table 42. FLU-Q-TIV-(b)(4)-008 –Percentage of Subjects in the FluLaval (b)(4) Group with Individual Solicited Local Adverse Reactions during the Four Days Post-Vaccination by Age Group (ATP Safety Cohort)

Type of Solicited Local Adverse Reaction	3-4 Years N=294	5-8 Years N=252	9-17 Years N=362
Any Pain	47%	65%	62%
Grade 3 Pain	1.7%	4.1%	1.4%
Any Redness	4.8%	7.8%	3.6%
Grade 3 redness (>100 mm)	0	0.5%	0
Any Swelling	3.1%	6.2%	5.0%
Grade 3 Swelling (>100 mm)	0	0.3	0

Source: BLA 125163/ SN 254, CSR Q-TIV-(b)(4)-008, Supplement 53, page 178-179.

Pain was reported in a lower percentage of subjects from 3 to 4 years of age, who might not have been able to verbalize pain as well as older children. There was less than 5% difference between the age groups for the other two solicited adverse events. The types of solicited systemic adverse reactions followed differed by age. Please see Section 6.1.12 for the tabular summary of solicited systemic adverse reactions for subjects younger than 5 years and for those 5 years of age and older.

8.5.4 Product-Disease Interactions

Not applicable

8.5.5 Product-Product Interactions

Not applicable

8.5.6 Human Carcinogenicity

Not applicable

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No safety concerns correlate with antibody response.

8.5.8 Immunogenicity (Safety)

No safety concerns correlate with antibody response.

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

8.6 Safety Conclusions

The most common adverse event reported in the study of FluLaval in children was pain at the injection site, which was reported in 59% of subjects. The unsolicited adverse events reported were consistent with illnesses common in pediatric populations. Serious adverse events were observed in less than 1% of subjects. There were no unexpected adverse events or increases in adverse events reported in this study, and the safety profile was similar to what is described in adults in the package insert.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Vaccination of female rates with FluLaval, at doses which were immunogenic, had no effects on fertility. There have been no studies of effect on fertility in humans. Reproductive and developmental studies have been performed in rats, and no safety signal was identified. However, there are no adequate and well-controlled studies in pregnant women. There were no pregnancies in the study included in this supplement.

Flulaval is labeled as Pregnancy Category B.

9.1.2 Use During Lactation

The vaccine has not been evaluated in nursing mothers and it is not known if FluLaval 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 FLU-Q-TIV-(b)(4)-008. Study FLU-Q-TIV-(b)(4)-008 was a Phase III, immunogenicity and safety study in children from 3 through 17 years of age.

The applicant has agreed to conduct an immunogenicity and safety study of FluLaval Quadrivalent in children 6 months through 35 months of age. The trial is to be an immunogenic non-inferiority comparing FluLaval Quadrivalent to a U.S.-licensed comparator. The PREA requirement for this age group was deferred, since waiting for the data from this study would delay the availability of FluLaval 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 FluLaval 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.

In summary, 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. The plan for pediatric studies in younger subjects is adequate.

9.1.4 Immunocompromised Patients

FluLaval has not been studied in immunocompromised patients.

9.1.5 Geriatric Use

No information on the use of FluLaval in elderly subjects was included in this supplement.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Not applicable

10. CONCLUSIONS

The clinical data submitted in the supplemental BLA support the effectiveness and safety of FluLaval when administered to children 3 years of age and older. Study FLU-Q-TIV-(b)(4)-008, a randomized, active-controlled trial of 2116 healthy children from 3 years through 17 years age provided the primary evaluation of effectiveness. In this study, immunologic non-inferiority to a U.S.-licensed comparator vaccine was demonstrated. In addition, the efficacy of FluLaval is further supported by a clinical endpoint study of Flulaval Quadrivalent in children from 3 to 8 years of age. In this study, the vaccine efficacy of FluLaval Quadrivalent was 55.4% with a lower bound 95% confidence interval of 39.1%.

The safety data demonstrated local reactogenicity comparable to a U.S.-licensed comparator (Fluzone) and generally consistent with other inactivated influenza vaccines, with pain at the injection site being the most common adverse reaction. Irritability, drowsiness, and decreased appetite were reported commonly post-vaccination in children from 3 years to < 5 years of age, while myalgia, fatigue, and headache were reported in children from 5 years to 17 years of age. The rates of these signs of systemic reactogenicity in children who received Flulaval were also comparable to the rates after a U.S.-licensed comparator vaccine. Overall, the review of the safety database did not identify any safety signals.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Influenza infects 5-20% of the population each year, resulting in a large number of outcomes with a wide range of severity, including up to 200K hospitalizations, 3-44K deaths in the US annually • Roughly 10% of hospitalizations result in death, mostly in elderly • Flu-related complications include pneumonia, secondary bacterial infections, exacerbation of underlying conditions • Morbidity/mortality highest among the very young, the elderly, and those with underlying medical conditions	• Influenza is a major cause of morbidity/mortality in the US • A substantial proportion of infections result in serious or life-threatening disease, particularly among high-risk groups such as young children and the elderly.
Unmet Medical Need	• There are currently only five influenza vaccines licensed in the U.S. for use in children. • The ACIP recommends yearly immunization of all U.S. children. • The effectiveness of inactivated influenza vaccines has been estimated to be approximately 59%, and there is an extensive record of safety • The neuraminidase inhibitor class of antivirals are 70-90% effective for post-exposure chemoprophylaxis; however, they must be given twice daily; are not available in intravenous formulations for the most ill patients; provide protection only during the time when administered; and resistance to this products is an increasing problem.	• There are not enough influenza vaccines available in children to meet the ACIP objective of vaccinating all children yearly against seasonal influenza
Clinical Benefit	• One clinical trial of FluLaval in children 3 to 17 years of age was included in this submission. In this trial, FluLaval was immunogenically non-inferior to a US licensed comparator. • The results of a second clinical endpoint trial of a vaccine made using the FluLaval manufacturing process this time with (FluLaval Quadrivalent) were also included in this trial. Vaccine efficacy (55.4%) of FluLaval Quadrivalent was demonstrated in children 3 to 8 years of age. The results of this trial were used to infer effectiveness of the trivalent formulation of FluLaval since both vaccines are manufactured using the same processes.	• The antibody response to FluLaval was non-inferior to that to an active comparator. • Vaccine efficacy was demonstrated in a related quadrivalent vaccine. These results are useful in the evaluation of the trivalent formulation since both vaccines are manufactured using the same processes and have overlapping components.
Risk	• The most substantial risks of vaccination with FluLaval are pain at the injection site. However, most episodes of pain are mild in severity and self-limited. • Drowsiness, irritability, and loss of appetite were seen in more than 10% of children younger than 5 years of age; and myalgia, fatigue and headache were seen in more than 10% of children from 5 to 17 years of age. These adverse reactions were also typically mild and resolved without treatment or sequelae. • The total clinical trial safety database for FluLaval in this supplement was 1055. Additionally there has been no safety concerns based on post-marketing surveillance since the licensure of FluLaval in 2006. • No other safety signals were apparent in the pediatric population.	• All the evidence indicates that the risk of vaccination with FluLaval is minor.
Risk Management	• The most common risks of vaccination with FluLaval, including local injection site reactions and systemic reactogenicity, are mild and self-limited.	• If Flulaval were approved for children 3 to 17 years, routine measures, such as the package insert and the current pharmacovigilance plan, would be adequate to manage the risks

11.2 Risk-Benefit Summary and Assessment

The data submitted in this application support the clinical efficacy of FluLaval in children. These data, combined with the immunogenicity data, support the effectiveness of FluLaval in children from 3 through 17 years of age. The observed risks of vaccination of FluLaval in children were primarily solicited local and systemic reactions that were mild and self-limiting; these risks will be described in the package insert. In the opinion of this reviewer, FluLaval therefore presents a favorable overall risk-benefit profile.

11.3 Discussion of Regulatory Options

In the opinion of this reviewer, the efficacy data from FluLaval Quadrivalent and the immunogenicity and safety data from FluLaval support the traditional approval of FluLaval in individuals 3 years of age and older. FLU-Q-QIV-006 is the first pediatric clinical endpoint study of an inactivated influenza vaccine used to verify effectiveness of an influenza vaccine approved under accelerated approval. Given the complexities and the increased difficulties of a prospective randomized clinical trial to demonstrate effectiveness in a pediatric population, this was deemed an acceptable approach to verifying effectiveness of trivalent FluLaval. After full review of the data in this supplement, no other regulatory options, besides approval, were discussed for this product.

11.4 Recommendations on Regulatory Actions

The immunogenicity and safety of FluLaval were compared to that of a U.S.-licensed influenza vaccine. The antibody responses to FluLaval were non-inferior to those to the comparator. The safety results were also similar in the two vaccine groups; the most frequently reported adverse reactions were pain at the injection site; drowsiness, irritability, and loss of appetite in subjects younger than 5 years; and muscle aches, fatigue, and headache in children 5 through 17 years of age. Adverse reactions were generally mild and self-limited. In addition, vaccine efficacy of 55% was demonstrated in a prospective, randomized, observer-blind, and controlled study of FluLaval Quadrivalent, which is manufactured using the same processes as the trivalent formulation of FluLaval. Therefore, in the opinion of this reviewer, the efficacy data from FluLaval Quadrivalent and the immunogenicity and safety data from FluLaval support the traditional approval of FluLaval in individuals 3 years of age and older.

11.5 Labeling Review and Recommendations

Revisions to the package insert were discussed with the applicant. The immunogenicity and safety data from Study FLU-Q-TIV-(b)(4)-008 and the efficacy data from FLU-Q-QIV-006 were added to the FluLaval package insert. The main issues discussed with the applicant were the inclusion of secondary endpoints and subgroup analyses from Study FLU-Q-QIV-006.

11.6 Recommendations on Postmarketing Actions

The applicant plans to conduct an immunogenicity and safety study comparing FluLaval to a U.S.-licensed comparator in children 6 to 35 months of age. The applicant also agreed to establish a pregnancy registry as a post-marketing commitment.