Summary Basis of Regulatory Action

Date: August 16, 2013

To: Wellington Sun, MD, DVRPA Director

Through: Rakesh Pandey, Ph.D., DVRPA Branch Chief
Tim Nelle, Ph.D., DVRPA Team Lead

From: Sara Gagneten, Ph.D., DVP, Committee Chair

BLA/ STN: 125163/254

Applicant Name: ID Biomedical Corporation of Quebec, dba GlaxoSmithKline Biologicals (GSK)

Date of Submission: October 17, 2012

PDUFA Goal Date: August 18, 2013

Proprietary Name: FluLaval®

Established Name: Influenza Virus Vaccine

Indication: FluLaval, Influenza Virus Vaccine, is indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B virus contained in the vaccine for use in persons 3 years of age and older.

Dosage Forms: Suspension for injection supplied in 5-mL multi-dose vials

Recommended Action: Approval

Signatory Authorities Action: Approval

Division Signatory Authority: Wellington Sun, M.D., Director, Division of Vaccines and Related Product Applications

☐ **I concur with the summary review.**
☐ **I concur with the summary review and include a separate review to add further analysis.**
☐ **I do not concur with the summary review and include a separate review.**

The documentation used as the basis for the content of the various disciplines covered in this SBRA is listed in the table below.

Specific documentation used as basis for the SBRA	**Reviewer – Date of Review**
Clinical Review	Melisse Baylor, M.D. - 8/16/13 Roshan Ramanathan, M.D. - 8/16/13
Pharmacovigilance Review	Craig Zinderman, M.D. - 8/5/13
Statistical Review, Clinical	Sang Ahnn, Ph.D. - 6/21/13
Biomedical Monitoring	Christine Drabick - 6/4/13
Labeling	Maryann Gallagher - 4/4/13 Laura Montague - 8/16/13
Communication and Documentation	Laura Montague - 8/16/13 Bernard McWatters Ph.D. - 8/16/13

Cross-referenced Applications:

- IND 110166 - Influenza Virus Trivalent (Types A and B) Inactivated Split Virion (chicken eggs) Vaccine
- STN 125163/253 – Supplement to support the quadrivalent formulation of FluLaval. The cross-reference information consists of: 1) results a clinical endpoint study (FLU Q-QIV-006) of FluLaval Quadrivalent in children 3 to 8 years of age; and 2) assay method and validation for the hemagglutination inhibition (HI) assay for determination of antibodies in human sera.

1. Introduction

FluLaval, a split virion trivalent influenza vaccine (TIV), contains the purified outer membrane protein hemagglutinin (HA), from each of the 3 influenza virus strains recommended annually by the World Health Organization (WHO) and the Center for Biologics Evaluation and Research (CBER). The FluLaval HA antigens are derived from viruses propagated in embryonated chicken eggs. It is presented as a suspension for injection, in a (b)(4) glass vial, containing a total of ten 0.5 mL doses. Each dose contains 45 micrograms (mcg or µg) HA in the recommended ratio of 15 mcg HA of each of the 3 influenza strains in a sterile, buffered aqueous suspension with thimerosal as a preservative.

Proposed Indication: "FluLaval, Influenza Virus Vaccine, is indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B virus contained in the vaccine. FluLaval is approved for use in persons 3 years of age and older."

Proposed Dosage: The dosage proposed for children 3 years to 17 years of age is 0.5 mL administered by intramuscular (IM) injection once or twice depending on age and vaccination

history. The preferred injection site is the deltoid muscle of the upper arm. The dose and schedule for FluLaval Quadrivalent are presented in Table 1.

Table 1. FluLaval Dosing

Age	Vaccination Status	Dose and Schedule
3 through 8 years of age	Not previously vaccinated with influenza vaccine	Two doses (0.5-mL each) at least 4 weeks apart
	Vaccinated with influenza vaccine in a previous season	One or two doses[a] (0.5-mL each)
9 years of age and older	Not applicable	One 0.5-mL dose

[a] One dose or two doses (0.5-mL each) depending on vaccination history as per the annual Advisory Committee on Immunization Practices (ACIP) recommendation on prevention and control of influenza with vaccines. If two doses, administer each 0.5-mL dose 4 weeks apart.

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2. Background

The data in this supplement are based on studies conducted under IND 11016, which was submitted on August 20, 2010. The major regulatory actions since approval of FluLaval are as follows:

Background: Selected Regulatory Actions

a. FluLaval was approved under the accelerated approval regulations (21 CFR 601.41) on October 5, 2006. The approval letter contained a post-marketing commitment (PMC) to conduct a non-inferiority study in adults ≥50 years of age; and a post-marketing requirement (PMR) to conduct a clinical endpoint study in adults 18 to 49 years of age.
b. A clarification letter was issued on June 1, 2011, containing PREA-related PMRs for: 1) a non-inferiority study comparing FluLaval to Fluzone in children 3 to 17 years of age; and 2) a clinical endpoint efficacy study of FluLaval Quadrivalent in children 3 to 8 years of age (see Items d and e below).
c. In STN 125163/176 the sponsor submitted results of the two clinical studies to address the PMC and PMR of the October 5, 2006, approval letter. Because the results of the clinical endpoint study did not demonstrate effectiveness, the accelerated approval PMR

was not fulfilled. To address this issue, the approval letter of June 9, 2011, contained a new PMR for a clinical endpoint study of FluLaval Quadrivalent in children 3 to 8 years of age (see Items d and e below). This reflected the agreement between CBER and GSK that the clinical endpoint study of FluLaval Quadrivalent in children 3 to 8 years of age could address both the PREA requirement with regard to Flulaval Quadrivalent *and* the PMR to verify clinical benefit and support traditional approval for the trivalent formulation.

d. Supplement STN 125163/253, approved on August 15, 2013, contains the results of the clinical endpoint study of FluLaval Quadrivalent in children 3 to 8 years of age to address the PMR in the letter of June 9, 2011 and was submitted concurrently with the current supplement, STN 125163/254. After approval of STN 125163/253, FluLaval Quadrivalent effectiveness will have been demonstrated and Flulaval Quadrivalent will have full approval for use in persons 3 years of age and older.

e. The current supplement, STN 125163/254, was submitted for approval of FluLaval (trivalent) for use in persons 3 years of age and older based on: 1) a non-inferiority study comparing FluLaval to Fluzone in children 3 to17 years of age (study FLU Q-TIV-(b)(4)-008); and 2) a cross-reference to STN 125163/253 for the efficacy endpoint study of FluLaval Quadrivalent in children. Therefore, after approval of STN 125163/253 and 125163/254, FluLaval effectiveness will have been verified and FluLaval will have full approval for use in persons 3 years of age and older. The efficacy experience with FluLaval Quadrivalent is applicable to FluLaval because the antigens in both vaccines are manufactured using the same process and the vaccines have overlapping compositions.

f. ----------(b)(4)----------.

3. Chemistry Manufacturing and Controls (CMC)

No CMC information was provided in this supplement.

- The following information for the two vaccines (FluLaval (b)(4) and comparator vaccine) used in the non-inferiority immunogenicity clinical study FLU Q-TIV-(b)(4)-008 was provided:

FluLaval (b)(4)
The FluLaval (b)(4) vaccine is a ----(b)(4)---- formulation of the approved trivalent thimerosal-containing FluLaval influenza virus vaccine.

FluLaval (b)(4) is a homogenized, sterile, colorless to slightly opalescent suspension in a phosphate buffered saline solution. FluLaval (b)(4) was standardized according to the US Public Health Service (USPHS) requirements for the Northern Hemisphere 2009-2010 influenza season and was formulated to contain 45 mcg hemagglutinin (HA) per 0.5 mL dose in the recommended ratio of 15 mcg HA of each of the following 3 strains:

A/Brisbane/59/2007 (H1N1),

A/Uruguay/716/2007 (H3N2) (an A/Brisbane/10/20070-like virus), and
B/Brisbane/60/2008.

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

Each dose may contain residual amounts of egg protein ((b)(4) ovalbumin), formaldehyde (≤25 μg), and sodium deoxycholate (≤50 μg).

Comparator Vaccine (Fluzone)
The trivalent inactivated influenza virus vaccine, Fluzone (Sanofi Pasteur, Inc.), was the comparator vaccine used in this study. The vaccine used in the trial contained HA from the three influenza virus strains recommended for 2009-10 (15 μg HA per strain; total HA = 45 μg). The virus strain composition was the same as for FluLaval (b)(4).

- The following FluLaval (b)(4) and Fluzone vaccine lots were administered in the clinical trial:
  FluLaval (b)(4): Lot # AFLLA263A
  Fluzone: Lot # U3253DA

- The quantitative composition of FluLaval per 0.5 mL dose is presented in Table 2 (this information was provided in -------(b)(4)------ for the production of FluLaval using ----------(b)(4)----------).

Table 2. Quantitative Composition of FluLaval Drug Product

Ingredients	**Quantity (per 0.5 mL dose)**	**Function**
Active substances		
Monovalent inactivated split-virion: A/H1N1	15 µg HA	Antigen
Monovalent inactivated split-virion: A/H3N2	15 µg HA	Antigen
Monovalent inactivated split-virion: B strain	15 µg HA	Antigen
Excipients		
----------(b)(4)----------	(b)(4)	---(b)(4)---
----------(b)(4)----------	(b)(4)	---(b)(4)---
Thimerosal	50 µg	Preservative
Phosphate Buffered Saline:		
Sodium chloride	(b)(4)	Buffer
Potassium chloride	(b)(4)	Buffer
Disodium hydrogen phosphate heptahydrate	(b)(4)	Buffer
Potassium dihydrogen phosphate	(b)(4)	Buffer
---(b)(4)	(b)(4)	(b)(4)

The vaccine contains -----(b)(4)------ 0.5mL dose) which is used as a -(b)(4)- for (b)(4). The vaccine may also contain the following residual reagents from the manufacturing process: formaldehyde, ovalbumin, (b)(4) and sodium deoxycholate.

Currently, FluLaval is presented only in 5 mL multidose vials with thimerosal. The thimerosal content of the vaccine is 100 µg/mL. This corresponds to <50 µg/mL of organic mercury, or <25 µg of organic mercury per 0.5-mL dose.

The FluLaval DS and drug product (DP) are manufactured by ID Biomedical Corporation of Quebec (IDB) doing business as GlaxoSmithKline Biologicals North America in the following location:

ID Biomedical Corporation of Quebec d/b/a GlaxoSmithKline Biologicals North America
2323 du Parc Technologique Blvd.
Sainte-Foy, Quebec
Canada G1P 4R8

The thimerosal-containing formulation of FluLaval may be produced from DS monovalent bulks manufactured with ----------(b)(4)----------. When the vaccine is formulated with ------(b)(4)------ bulks, ----------(b)(4)----------. The vaccine that is formulated with -------(b)(4)------- bulks does not contain the (b)(4) and ----------(b)(4)----------.

4. Nonclinical Pharmacology/Toxicology

Toxicology studies were performed to support the BLA application and previously submitted supplements. No toxicology studies were performed in support of the current supplement.

5. Clinical Pharmacology

No clinical pharmacology or pharmacokinetic studies were performed in the development program for FluLaval.

6. Clinical Effectiveness and Safety

6.1 Summary of Results

The conclusions about the safety and immunogenicity of FluLaval in children 3 to 17 years of age were based on the results of study FLU Q-TIV-(b)(4)-008, a phase 3 study submitted in the current supplement, 125163/254. Safety and efficacy data were also derived from study FLU Q-QIV-006, a phase 3 study in children 3 to 8 years of age. The results of this study were submitted to support supplement STN 125163/253 for the approval of a quadrivalent formulation of Flulaval and were cross-referenced in the current supplement STN 125163/254 (see Section 2, Items d and e). The efficacy experience with FluLaval Quadrivalent is applicable to FluLaval because the antigens in both vaccines are manufactured using the same process and the vaccines have overlapping compositions.

This memo includes a summary of the safety and immunogenicity results of study FLU Q-TIV-(b)(4)-008 and a summary of efficacy results of study FLU Q-QIV-006.

Immunogenicity and Safety Evaluation in Children (FLU Q-TIV-(b)(4)-008)

Safety Results - Study FLU Q-TIV-(b)(4)-008 (NCT 00980005) was an observer-blind, active-controlled study. It evaluated subjects 3 to 17 years of age who received FluLaval (b)(4) (N = 1,055) or Fluzone (N = 1,061), a US-licensed trivalent, inactivated influenza virus vaccine manufactured by Sanofi Pasteur SA. In the overall population, 53% were male; 78% of subjects were White, 12% were Black, 2% were Asian, and 8% were of other racial/ethnic groups. The mean age of subjects was 8 years. Children 3 to 8 years of age with no history of influenza vaccination received 2 doses approximately 28 days apart. Children 3 to 8 years of age with a history of influenza vaccination and children 9 years of age and older received one dose. Solicited local adverse reactions and systemic adverse events were collected for 4 days (day of vaccination and the next 3 days) (Table 3).

Table 3. Incidence of Solicited Local Adverse Reactions and Systemic Adverse Events within 4 Days[a] of First Vaccination in Children 3 to 17 Years of Age[b] (Total Vaccinated Cohort)

	FluLaval (b)(4) %	Active Comparator[c] %
	3 to 17 Years of Age	
Local Adverse Reactions	**N = 1,042**	**N = 1,026**
Pain	56	53
Redness	4	5
Swelling	4	5
	3 to 4 Years of Age	
Systemic Adverse Events	**N = 293**	**N = 279**
Irritability	25	27
Drowsiness	19	19
Loss of appetite	16	13
Fever ≥100.4°F (38.0°C)	5	3
	5 to 17 Years of Age	
Systemic Adverse Events	**N = 750**	**N = 747**
Muscle aches	24	23
Headache	17	15
Fatigue	17	17
Arthralgia	8	10
Shivering	6	5
Fever ≥100.4°F (38.0°C)	5	4

Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were available.

[a] 4 days included day of vaccination and the subsequent 3 days.

[b] Study 4: NCT00980005.

[c] US-licensed trivalent, inactivated influenza virus vaccine (manufactured by Sanofi Pasteur SA).

In children who received a second dose of FluLaval (b)(4) or the comparator vaccine, the incidences of adverse events following the second dose were generally lower than those observed after the first dose.

The incidence of unsolicited adverse events that occurred within 28 days (day 0-27) of any vaccination reported in subjects who received FluLaval (b)(4) (N = 1,055) or Fluzone (N = 1,061) was 40% and 37%, respectively. The unsolicited adverse events that occurred most frequently (≥0.1% of subjects for FluLaval) and considered possibly related to vaccination included diarrhea, influenza-like illness, injection site hematoma, injection site rash, injection site warmth, rash, upper abdominal pain, and vomiting. The rates of serious adverse events (SAE) were comparable between groups (0.9% and 0.6% for FluLaval and the comparator, respectively); none of the SAEs were considered related to vaccination. No safety signal was identified in the review of this study.

Immunogenicity Results - In Study FLU Q-TIV-(b)(4)-008 the immune response of FluLaval (b)(4) (N = 987) was compared to Fluzone (N = 979). The immune responses to each of the antigens contained in FluLaval (b)(4) formulated for the 2009-2010 season were evaluated in sera

obtained after one or 2 doses of FluLaval (b)(4) and were compared to those following the comparator influenza vaccine.

The non-inferiority endpoints were geometric mean antibody titers (GMTs) adjusted for baseline, and the percentage of subjects who achieved seroconversion, defined as at least a 4-fold increase in serum hemagglutination inhibition (HI) titer over baseline to ≥1:40, following vaccination, performed on the according-to-protocol (ATP) cohort. FluLaval (b)(4) was non-inferior to Fluzone for all strains based on adjusted GMTs and seroconversion rates (Table 4). All immunogenicity primary endpoints were met.

Table 4. Immune Responses to Each Antigen 28 Days After Last Vaccination with FluLaval (b)(4) Versus Comparator Influenza Vaccine in Children 3 to 17 Years of Age[a] (According to Protocol Cohort for Immunogenicity)[b]

	FluLaval (b)(4)	**Active Comparator[c]**	
GMTs Against	**N = 987 (95% CI)**	**N = 979 (95% CI)**	**GMT Ratio[d] (95% CI)**
A/Brisbane (H1N1)	320.9 (298.3, 345.2)	329.4 (306.8, 353.7)	1.03 (0.94, 1.13)
A/Uruguay (H3N2)	414.7 (386.5, 444.9)	451.9 (423.8, 481.8)	1.05 (0.96, 1.13)
B/Brisbane	213.7 (198.5, 230.1)	200.2 (186.1, 215.3)	0.93 (0.85, 1.02)
Seroconversion[e] to:	**N = 987 % (95% CI)**	**N = 978 % (95% CI)**	**Difference in Seroconversion Rate[f] (95% CI)**
A/Brisbane (H1N1)	59.8 (56.6, 62.9)	58.2 (55.0, 61.3)	-1.6 (-5.9, 2.8)
A/Uruguay (H3N2)	68.2 (65.2, 71.1)	66.2 (63.1, 69.1)	-2.0 (-6.1, 2.1)
B/Brisbane	81.1 (78.5, 83.5)	78.6 (75.9, 81.2)	-2.4 (-6.0, 1.1)

GMT = geometric mean antibody titer; CI = Confidence Interval.

[a] Results obtained following vaccination with influenza vaccines formulated for the 2009-2010 season.

[b] The according to protocol cohort for immunogenicity included all evaluable subjects for whom assay results were available after vaccination for at least one study vaccine antigen.

[c] US-licensed trivalent, inactivated influenza virus vaccine (Sanofi Pasteur SA).

[d] FluLaval (b)(4) met non-inferiority criteria based on GMTs (upper limit of 2-sided 95% CI for GMT ratio [comparator vaccine/FluLaval (b)(4)] ≤1.5).

[e] Seroconversion defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer ≥1:10, or an increase in titer from <1:10 to ≥1:40.

[f] FluLaval (b)(4) met non-inferiority criteria based on seroconversion rates (upper limit of 2-sided 95% CI for difference of the comparator vaccine minus FluLaval (b)(4) ≤10%).

Clinical Endpoint Efficacy Study in Children (FLU Q-QIV-006)

The results of study FLU Q-QIV-006 were submitted to support supplement STN 125163/253 for the approval of a quadrivalent formulation of Flulaval and were cross-referenced in the current supplement, STN 125163/254 (see Section 2, Items d and e). The efficacy experience with FluLaval Quadrivalent is applicable to FluLaval because the antigens in both vaccines are manufactured using the same process and the vaccines have overlapping compositions.

Efficacy Results - The efficacy of FluLaval Quadrivalent was evaluated in Study FLU Q-QIV-006, a Phase 3, randomized, observer-blind, non-influenza vaccine-controlled study conducted in 3 countries in Asia, 3 in Latin America, and 2 in the Middle East/Europe during the 2010-2011 influenza season. Healthy subjects 3 to 8 years of age were randomized (1:1) to receive: 1) FluLaval Quadrivalent (N = 2,584), containing A/California/7/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/4/2006 (Yamagata lineage) influenza strains; or 2) Havrix (N = 2,584), a US-licensed hepatitis A vaccine manufactured by GSK, as a control. Children with no history of influenza vaccination received 2 doses of FluLaval Quadrivalent or Havrix approximately 28 days apart. Children with a history of influenza vaccination received one dose of FluLaval Quadrivalent or Havrix.

Efficacy of FluLaval Quadrivalent was assessed for the prevention of reverse transcriptase polymerase chain reaction (RT-PCR)-confirmed influenza A and/or B disease presenting as influenza like illness (ILI). ILI was defined as a temperature ≥100°F in the presence of at least one of the following symptoms on the same day: cough, sore throat, runny nose, or nasal congestion. Subjects with ILI (monitored by passive and active surveillance for approximately 6 months) had nasal and throat swabs collected and tested for influenza A and/or B by RT-PCR. All RT-PCR-positive specimens were further tested in cell culture. Vaccine efficacy was calculated based on the ATP cohort for efficacy (Table 5).

Table 5. FluLaval Quadrivalent: Influenza Attack Rates and Vaccine Efficacy against Influenza A and/or B in Children 3 to 8 Years of Age[a] (According to Protocol Cohort for Efficacy)

	N[b]	n[c]	Influenza Attack Rate % (n/N)	Vaccine Efficacy % (CI)
All RT-PCR-Positive Influenza				
FluLaval Quadrivalent	2,379	58	2.4	55.4[d] (95% CI: 39.1, 67.3)
Havrix[e]	2,398	128	5.3	–
All Culture-Confirmed Influenza[f]				
FluLaval Quadrivalent	2,379	50	2.1	55.9 (97.5% CI: 35.4, 69.9)
Havrix[e]	2,398	112	4.7	–
Antigenically Matched Culture-Confirmed Influenza				
FluLaval Quadrivalent	2,379	31	1.3	45.1[g] (97.5% CI: 9.3, 66.8)
Havrix[e]	2,398	56	2.3	–

CI = Confidence Interval; RT-PCR = reverse transcriptase polymerase chain reaction.

[a] Study 3: NCT01218308.

[b] According to protocol 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.

[c] Number of influenza cases.

[d] Vaccine efficacy for FluLaval Quadrivalent met the pre-defined criterion of >30% for the lower limit of the 2-sided 95% CI.

[e] Hepatitis A Vaccine used as a control vaccine.

[f] 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 Quadrivalent; 37 with Havrix), and 2 cases B Victoria (2 with Havrix)].

[g] Since only 67% of cases could be typed, the clinical significance of this result is unknown.

In an exploratory analysis by age, vaccine efficacy against RT-PCR-positive influenza A and/or B disease presenting as ILI was evaluated in subjects 3 to 4 years of age and 5 to 8 years of age; vaccine efficacy was 35.3% (95% CI: -1.3, 58.6) and 67.7% (95% CI: 49.7, 79.2), respectively. As the study lacked statistical power to evaluate efficacy within age subgroups, the clinical significance of these results is unknown.

6.2 Statistical Review - Summary of Results

Study FLU Q-TIV-(b)(4)-008 was performed as pre-specified. The primary immunogenicity objective was met [immunogenic non-inferiority (in terms of Geometric Mean Titer [GMT] ratio and Seroconversion Rate [SCR]) of FluLaval (b)(4) compared to Fluzone in children 3 to 17 years old]. FluLaval (b)(4) and Fluzone appear to have similar safety profiles in children 3 to 17 years old. No major statistical issue was identified.

6.3 Clinical Assays

In clinical study FLU Q-TIV-(b)(4)-008 all subjects were vaccinated with either FluLaval (b)(4) or Fluzone and antibody response was evaluated in all subjects.

Hemagglutination Inhibition (HI) Assay
In study FLU Q-TIV-(b)(4)-008 the HI assay was used to measure the humoral immune response against each of the influenza strains contained in the FluLaval (b)(4) or Fluzone vaccines.

The HI assays were performed in GSK's (b)(4) laboratory. HI validation was performed in GSK's -(b)(4)- Laboratory and approved under 125127/513 for Fluarix Quadrivalent. Adequate documentation was provided to validate the HI assay in GSK's (b)(4) Laboratory in the cross-referenced supplement for FluLaval Quadrivalent (STN 125163/253).

To perform the HI assay, serial dilutions of serum samples are mixed with a standard solution of antigen (influenza virus) and red blood cells (RBCs). Serum antibodies, if present, will limit the RBC agglutination in proportion to their concentration. The starting dilution of the sera on the first row of the titration plate is ----------(b)(4)----------.

6.4 Pediatric Research Equity Act (PREA)

The PREA rule does not apply to this supplement because it does not involve a new indication, new active ingredient, new dose form, new dosing regimen or new route of administration. However, GSK's Pediatric Plan was presented to the FDA Pediatric Review Committee (PeRC) on May 8, 2013 because the current supplement and the cross-referenced supplement (STN 125163/254) fulfilled the two PMRs in the June 1, 2011 clarification letter issued by CBER (see Section 2 - Background). The following recommendations were accepted by the committee, and will be included in the approval letter as follows:

1. Waiver of the pediatric study requirement in infants 0 to < 6 months of age, because this product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of infants < 6 months of age.

2. Deferral of submission of the studies for ages 6 months to < 3 years for this application because this product is ready for approval for use in persons 3 years of age and older and the sponsor has committed to conduct a study in this age group. The timeline for submission of the protocol and final report for this required study were agreed upon with the manufacturer (see Section 9.4 - Recommendations for Postmarketing Activities).

6.5 Biomonitoring Review

CBER Bioresearch Monitoring (BIMO) issued inspection assignments covering four clinical study sites. The BIMO inspections did not reveal problems that would impact the data submitted in this supplement.

7. Advisory Committee Meeting

A Vaccines and Related Biological Products Advisory Committee meeting for discussion of the data in this submission was not held because our review did not raise concerns which would have benefited from an advisory committee discussion.

8. Labeling

The package insert (PI) was reviewed by the clinical and statistical reviewers and reviewers from the Advertising and Promotional Labeling Branch. In addition to the changes in the *Indications and Usage* and the *Dosage and Administration* sections, related to the use of FluLaval in children 3 to 17 years of age, the major changes to the PI were as follows:

- Package Insert:
  - *Dosage and Administration* section: The dosing schedule for children 3 to 17 years of age was included. For children 3 to 8 years of age the dosing schedule reflects the recommendations from the Advisory Committee on Immunization Practices (ACIP): children in this age group, not previously vaccinated should receive 2 doses, and those previously vaccinated should receive 1 or 2 doses.
  - *Adverse Reactions* section: The safety data from pediatric study FLU Q-TIV-(b)(4)-008 were placed after the summary of results from three adult studies which were included in the previously approved FluLaval label.
  - *Clinical Studies* section: The previously approved FluLaval label contained data from efficacy and immunogenicity studies in adults only. In the proposed label, the new efficacy data for FluLaval Quadrivalent in children (cross-reference to STN 125163/253) were presented before the efficacy data in adults. CBER and GSK agreed that the package insert could include a table comparing the number of cases of specific adverse outcomes (e.g., fever, wheezing, shortness of breath) among the RT-PCR-positive subjects in the FLU Q-QIV-006 study groups. The agreed upon text included a statement on the risk reduction of fever >102.2°F/39.0°C associated with RT-PCR-positive influenza infection in the vaccinated group as compared to the control group. The immunogenicity data from the non-inferiority pediatric study, FLU Q-TIV-(b)(4)-008, were presented after the immunogenicity data from studies in adults.

The applicant will submit the label in Structured Product Labeling (SPL) format after approval.

9. Recommendations and Risk/Benefit Assessment

9.1 Recommended Regulatory Action

Following the review of all supportive product and clinical data, it is the recommendation of the review committee to approve this BLA supplement for the use of FluLaval in children 3 to 17 years of age.

9.2 Risk/ Benefit Assessment

The clinical information submitted in this supplement together with the efficacy data for the clinical endpoint efficacy study of FluLaval Quadrivalent (cross-referenced supplement STN 125163/253) support the safety and effectiveness of FluLaval when administered to persons 3 years of age and older. The risks of vaccination with FluLaval are minimal, and the morbidity and mortality associated with influenza infection are substantial.

The clinical recommendation for the approval of FluLaval is based on the demonstration of non-inferiority for the three influenza strains in FluLaval compared to Fluzone. Additionally, clinical efficacy and safety in subjects 3 to 8 years of age were demonstrated in a study of Flulaval Quadrivalent. The safety concerns with FluLaval are primarily: 1) pain at the local injection site in all subjects; 2) irritability, drowsiness, and loss of appetite in children 3 to 4 years of age and muscle aches, head aches and fatigue in children 5 to 17 years of age. There were no individual adverse events or pattern of adverse events that suggested a safety signal associated with the administration of FluLaval. Therefore, the potential benefits of administration of FluLaval outweigh the potential risks.

9.3 Recommendation for Post-marketing Risk Management Activities

There was no recommendation for post-marketing risk management activities. See Section 9.4 for the post-marketing activities associated with the licensure of this product.

A pregnancy registry to collect data on spontaneously reported exposures to FluLaval during pregnancy is already in place for FluLaval.

9.4 Recommendation for Post-marketing Activities

Post-marketing activities include studies that will be performed post-licensure. These studies are classified as either postmarketing requirements under Section 505B(a) of the Food Drug and Cosmetic Act (FDCA), or postmarketing commitments subject to 21 CFR 601.70. The following post-marketing activities are included in the approval letter:

Post-marketing Study Subject to Reporting Requirements of 21 CFR 601.70

Deferred post-marketing pediatric study required under 505B(a) of the Federal Food, Drug, and Cosmetic Act:

- Deferred pediatric study under PREA to assess the non-inferior immunogenicity of FluLaval® Quadrivalent to a licensed influenza vaccine in children 6 to 35 months of age.

  Protocol Submission Date: June 30, 2014
  Study Completion Date: September 30, 2015
  Final Report Submission: March 31, 2016

9.5 Summary of Recommendations

The data in this supplement support the approval of FluLaval for the active immunization of persons 3 years of age and older for the prevention of influenza disease caused by influenza A subtype viruses and type B virus contained in the vaccine. The recommendation for the approval of FluLaval in pediatric patients is based on the non-inferior antibody response when FluLaval was compared to a U.S. licensed vaccine, demonstration of Flulaval Quadrivalent vaccine efficacy (cross-referenced supplement STN 125163/253), and the acceptable safety profile in which most adverse reactions were mild and self-limited.