Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology

MEMORANDUM

To:	Christopher Jankosky, MD, MPH Acting Director, Division of Epidemiology (DE), Office of Biostatistics and Epidemiology (OBE), Center for Biologics Evaluation and Research (CBER)
Through:	Meghna Alimchandani, MD Acting Chief, Pharmacovigilance Branch, DE, OBE, CBER
From:	Craig Zinderman, MD, MPH Associate Director of Product Safety, DE, OBE, CBER
Subject:	Pediatric Safety and Utilization Review for the Pediatric Advisory Committee (PAC) Meeting
Sponsor:	ID Biomedical Corporation of Quebec
Product:	FluLaval (Influenza Virus Vaccine)
BLA:	125163
Indication:	For active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. FluLaval is approved for use in persons 3 years of age and older.
Meeting Date:	April 12, 2016

1. INTRODUCTION

1.1 Product Description

FluLaval is a seasonal, inactivated, split-virion, trivalent influenza vaccine (TIV) that has been licensed and distributed in the U.S. since 2006 for prevention of influenza. Trivalent (three-strain) influenza vaccines protect against the strains expected to be predominant in a given year - two A virus strains most common in humans and a B strain. FluLaval, which is also marketed outside of the United States as Fluviral or GripLaval (hereafter referred to as FluLaval for the purposes of this review) contains 15mcg hemagglutinin (HA) per strain, for a total of 45mcg HA per 0.5 ml dose. FluLaval is supplied in 0.5-mL single dose prefilled syringes and in 5-mL multi-dose (10 doses) vials.

Specific vaccine strain composition for all seasonal influenza vaccines are determined annually by the FDA's Vaccines and Related Biological Products Advisory Committee, taking into consideration recommendations from the World Health Organization. The Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) provides and periodically updates recommendations for use of seasonal influenza vaccinations.[1]

1.2 Regulatory History

On October 5, 2006, the US Food and Drug Administration (FDA) granted accelerated approval of FluLaval to ID Biomedical Corporation of Quebec (a subsidiary of GlaxoSmithKline Biologicals (GSK)) for active immunization for the prevention of disease caused by influenza viruses subtypes A and B contained in the vaccine for adults 18 years of age or older. Based on confirmatory studies, the FDA, on August 16, 2013 granted traditional approval of FluLaval and approved expanded age usage for FluLaval to include individuals 3 years of age and older. FDA has not required any postmarketing studies of FluLaval in the approved age range for any safety reason. A pregnancy registry which was established in 2011 is ongoing and has not identified any safety issues to date.

FluLaval was first licensed December 18, 1992 in Canada, and it is marketed in 16 countries (as of June 30, 2012).

2. OBJECTIVE

The objective of this memorandum for the Pediatric Advisory Committee (PAC) is to present a comprehensive review of the postmarketing pediatric safety covering a period of 18 months following the August 16, 2013 approval for expanded age usage in accordance with Section 505B (i) (1) of the Food and Drug Cosmetic Act [21 U.S.C. §355c]. The trigger for this Pediatric postmarket safety review is the August 16, 2013 approval of FluLaval for expanded age usage in individuals 3 years and older. This review covers the period from August 16, 2013 through June 30, 2015.

An abbreviated presentation of this review to the PAC is planned for this product as it does

not meet the criteria that would necessitate a full oral presentation or a justified abbreviated presentation. Specifically, no new safety signals have been identified and no pediatric deaths were reported in the review period for FluLaval. The product does not have a Postmarketing Requirement for a post-approval safety study or Risk Evaluation and Mitigation Strategy. Although the PAC presentation is abbreviated, the analysis of the safety data is comprehensive, and this memorandum documents FDA's full and complete evaluation, including review of adverse event reports in passive surveillance data, Periodic Safety Reports from the manufacturer, data mining, and a review of the published literature.

3. MATERIALS REVIEWED

3.1 Vaccine Adverse Events Reporting System (VAERS)

- VAERS reports for FluLaval submitted July 1, 2010 - June 30, 2015

3.2 Manufacturer's Submissions

- Product distribution data
- FluLaval Risk Management Plan/Pharmacovigilance Plan Version 1:10, dated September 2012
- FluLaval Periodic Benefit Risk Evaluation Reports (PBRERs) for reporting intervals 12/18/2012-12/17/2013 and 12/18/2013-12/17/2014.
- FluLaval Prescribing Information last revised June 2015

3.3 FDA Documents

- FluLaval Approval Letter, dated August 16, 2013

3.4 Publications (See end notes)

4. LABEL CHANGES IN REVIEW PERIOD

There were no label changes related to safety concerns during the review period.

5. PRODUCT UTILIZATION DATA

According to the manufacturer, approximately 13.1 million doses of FluLaval were distributed in the US from August 16, 2013 to June 30, 2015. With respect to distribution since initial U.S. licensure (in 2006), approximately 123 million doses of FluLaval were distributed in the U.S. between January 2007 (the earliest date for which distribution data is available) and June 30, 2015. Note that the number of doses distributed is an estimate of the number of patients vaccinated because individuals may receive more than one dose and doses may have been distributed without being administered to patients. No data are available for pediatric-specific utilization.

According to the manufacturer's most recent periodic safety report (December 18, 2013-December 17, 2014), over 210 million doses of FluLaval have been distributed worldwide since the product's initial launch in 1992.

6. PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

This section describes GlaxoSmithKline's pharmacovigilance plan (PVP) for FluLaval. PVP's include the manufacturer's assessment of identified and potential risks based on pre-licensure clinical trials, post-market safety monitoring, published literature, known product-class effects, and other relevant sources of safety information. There were no important identified risks for FluLaval from pre-licensure clinical studies or from post-market safety monitoring.

Potential risks included by the sponsor for FluLaval are consistent with potential risks for most seasonal influenza vaccines, and these risks include anaphylaxis, Bell's palsy, febrile seizure, Guillain-Barré syndrome, and injection site hemorrhage in individuals with thrombocytopenia or any coagulation disorder.

The PVP notes that these adverse events were included as potential risks due to previous documented association of each of these events with a particular influenza vaccine. Febrile seizures were detected in young children in Western Australia in association with another seasonal vaccine in 2010.[2,3] Bell's palsy has been associated with use of an E. coli heat-labile toxin-containing intranasal inactivated influenza vaccine, never licensed or distributed within the US, which was withdrawn from the market, although a subsequent, well-designed epidemiological study did not show an association with other inactivated influenza vaccines and the development of Bell's palsy.[4,5] Guillain-Barré Syndrome (GBS) was associated with use of an A/New Jersey 1976 influenza vaccine in anticipation of a swine influenza epidemic.[6] A subsequent case-control study found a relative incidence of GBS within 90 days following influenza vaccination of 0.75 (95% CI, 0.41 to 1.40), while the relative incidence of GBS within 90 days following an influenza-like illness was 7.35 (95% CI, 4.36 to 12.38), with the greatest relative incidence (16.64; 95% CI, 9.37 to 29.54) within 30 days following illness.[7] Based on a review of epidemiologic and mechanistic evidence, the Institute of Medicine's Committee to Review Adverse Effects of Vaccines concluded in 2012 that the evidence is inadequate to accept or reject a causal relationship between influenza vaccine and Guillain-Barré syndrome.[8]

In 2014, the manufacturer added narcolepsy as a potential risk to its Risk Management Plan (RMP) in Europe (the RMP is the pharmacovigilance plan document used in Europe) for all of its H1N1-containing influenza vaccines, noting that this change was a precautionary measure based on epidemiological studies that reported an increased risk of narcolepsy in subjects who received GSK's pandemic vaccine, Pandemrix. The sponsor notes that there is no clinical evidence of increased risk of narcolepsy for GSK H1N1-containing seasonal influenza vaccines, including FluLaval.

A pregnancy registry was established in September 2011 for FluLaval, and subsequently was combined into a single registry for all of GSK's inactivated influenza vaccine (IIV) products (Fluarix, FluLaval, Fluarix Quadrivalent, and FluLaval Quadrivalent). The registry prospectively enrolls women who receive FluLaval or one of the other IIV products during pregnancy and report no adverse events at the time of enrollment. These individuals will be prospectively followed to evaluate outcomes including pregnancy outcome, method of delivery, fetal/neonatal status, including description of birth defects if applicable, gestational weeks at birth/miscarriage/termination, sex, length, weight, Apgar score, additional drug/vaccine exposure including drug/vaccine name, route of administration, dose, lot number,

indication and date of administration, and AEs experienced by the fetus/infant or the mother. Enrollment will continue after submission of the final study report (anticipated in 2020) until FDA review and determination that the registry can be discontinued. As of 12/17/14 (data lock point of the sponsor's most recent PBRER), 99 pregnancies were prospectively reported to the registry with exposure to FluLaval, 66 of which were lost to follow-up. Of the remaining pregnancies, the observed outcomes were similar to expected frequencies of these outcomes in pregnancy, including 27 live births without congenital anomalies, 1 spontaneous abortion, 5 ongoing (including one case diagnosed in utero with cleft lip and palate).

There are no other completed or outstanding postmarketing safety study commitments or requirements to address safety concerns for FluLaval. Under the Pediatric Research Equity Act (PREA) the sponsor is required to conduct a study to evaluate the safety and immunogenicity of their quadrivalent vaccine, FluLaval Quadrivalent, in children 6 months to 35 months of age. The sponsor's PBRERs do not suggest any change in FluLaval's overall benefit-risk profile. The sponsor has not identified any new safety signals, nor any additional identified risks that were not already identified at the time of approval of the expanded age for use to include persons 3 years and older.

7. ADVERSE EVENT REVIEW

7.1 Methods

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event reports following use of FluLaval between August 16, 2013 and June 30, 2015. Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. VAERS was also queried for adverse events following FluLaval use for the past 5 years (from July 1, 2010 through June 30, 2015) to assess the historical frequency and nature of adverse event reporting for FluLaval prior to the August 13, 2013 approval for use in patients 3 years and older.

7.2 Results

The results of the VAERS search of adverse events for FluLaval during the review period are listed in Table 1, below. Deaths and serious reports are reviewed in detail in sections 7.2.1, 7.2.2 and 7.2.3.

Table 1: VAERS reports for FluLaval (August 16, 2013 through June 30, 2015)

Age (Years)	Serious Non-Fatal (includes OMIC)*			Deaths			Non-Serious			Total		
	US	Non-US	Total	US	Non-US	Total	US	Non-US	Total	US	Non-US	Total
<3	1	0	1	0	0	0	6	0	6	4	0	4
3-17	2	2	4	0	0	0	27	0	27	32	2	34
≥18	44	5	49	1	0	1	341	1	342	386	6	392
Unknown	11	13	14	1	0	1	47	0	47	59	3	62
Total	58*	10	68*	2	0	2	421	1	422	481	11	492

*Serious adverse events (including Otherwise Medically Important Conditions (OMIC)) are defined in 21CFR600.80.

Table 1 summarizes the 492 adverse event reports submitted during the review period to VAERS for FluLaval, overall and by age. A total of 38 pediatric reports, included five non-fatal serious reports, involved children 0 through 17 years of age.

7.2.1 Deaths

No pediatric deaths were reported following vaccination with FluLaval.

Adult deaths

Two adult deaths were reported in the review period. A 66year old male with a history of hypertension, diabetes, hyperlipidemia, and aortic valve disorder received FluLaval on 11/6/2013 and died (b) (6) . The death certificate lists cause of death as cardiac arrhythmia. No further details were reported. In the second case, a male of unknown age received FluLaval in 2013 and died 2 months later. Past medical history, cause of death,

and other details were not reported.

7.2.2. Non-fatal serious reports
Non-fatal Serious Adverse Events in Children 0-17 years of age
One report described exposure of an infant to FluLaval through breast milk. The infant (of unknown age) was breastfed one day after the mother received FluLaval on 10/24/2014 and subsequently developed diarrhea after an unreported time. Further details were not reported.

A 5 year old female in Canada received FluViral on an unknown date and experienced vesicles, erythema, pruritus, and swelling at the injection site at an unknown time after vaccination and was hospitalized. No further details were available.

A 5 year old male in Canada was vaccinated with FluViral on 11/5/2013 and 2 days later experienced itching, erythema, warmth, and induration at the injection site, with swelling in the arm and shoulder. Three days after vaccination a physician assessed the patient's reaction as cellulitis or allergic reaction. The patient was also diagnosed with otitis and treated with antibiotics for cellulitis and otitis.

A 13 year old female with a history of allergy to bee stings received FluLaval on 1/6/2014. Within minutes she complained of dizziness, shivering, headache, chest tightness, shortness of breath, "puffy face", flushing, dry throat, and strange sensation on tongue. Patient presented to an Emergency Department (ED) where she was found to be mildly hypotensive; she did not have rash, wheezing, or obvious facial or peri-oral edema. She was treated as an outpatient with epinephrine, after which she experienced immediate improvement, and diphenhydramine and a 4 day course of steroids. The ED diagnosis was allergic reaction.

A 17 year old male received FluLaval on 10/15/2013 and in less than 2 hours after vaccination experienced sudden severe headache and chills, followed by nausea for 2 days and jaundice. The patient was evaluated at an Emergency Department on the day of vaccination and found to have neutropenic fever and thrombocytopenia and was hospitalized. Hospital records indicated headache, neutropenia, fever, thrombocytopenia and erythematous rash. The patient was treated with intravenous fluids, fever, pain control; his symptoms resolved within 24 hours and he was discharged home the next day. The discharge diagnosis was dehydration or possible viral exanthema with transient viremia.

7.2.3 Non-serious Reports
During the reporting period there were 421 non-serious adverse events, 33 of which involved individuals <18 years old. Most non-serious reports were for labeled events and were consistent with the known safety profile of influenza vaccines. In the pediatric age group the most commonly reported adverse events were: Injection site erythema (N=7), Injection site swelling (N=5), and Drug administered to patient of inappropriate age (N=4; none of these reports identified an adverse event). No other adverse event terms occurred in more than 3 pediatric reports.

7.2.4 Historical VAERS Data (July 1, 2010- June 30, 2015)

Table 1: VAERS reports for FluLaval (July 1, 2010- June 30, 2015)

Age Group	Serious Non-Fatal (includes OMIC)			Deaths			Non-Serious			Total		
	US	Non-US	Total	US	Non-US	Total	US	Non-US	Total	US	Non-US	Total
<3	1	1	2	0	0	0	10	0	12	11	1	12
3 – 17	4	6	10	0	0	0	93	0	80	97	6	103
≥18	241	20	261	10	0	10	1556	2	1611	1807	22	1829
Unknown	18	8	26	2	2	4	153	1		173	11	184
Total	264	35	299	12	1	14	1812	3	1703	2088	40	2128

Twelve serious reports were received in children under 18 years old over the 5 year historical period. Most adverse event terms among pediatric cases over this period are labelled events and are consistent with the known safety profile of influenza vaccines. The most common events were fever (n=4) and cellulitis (n=3). No other adverse event terms appeared in more than 2 pediatric cases. No substantive differences were observed between the historical period and the recent review period (August 16, 2013 and June 30, 2015) with respect to the types and frequencies of adverse events reported.

7.3 Data Mining

Data mining was conducted using Empirica Signal software version 7.2 to evaluate whether any events following use of FluLaval were disproportionally reported, compared to other vaccines in the VAERS database. Data mining findings are subject to a number of potential limitations and do not imply causality. Disproportionality alerts do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation.

No data mining alerts for disproportional reporting were identified for FluLaval during the 2013-2014 influenza vaccination season (via query of Empirica Signals Management on 3/24/2015 with data recent as of 3/3/2014). For the 2014-2015 influenza vaccination season (via query run with data available through 9/2/2015), disproportional reporting alerts were identified for FluLaval for the following adverse event preferred terms (PTs):

- *Hypoglycemia* and *Product quality issue*

Both of these PTs stem from a cluster of six VAERS cases that were reported to CDC from a public school in Missouri where a school nurse vaccinated several adult employees on 9/26/2014. (Five of the six cases were vaccinated on the same day; one case had similar but less severe symptoms after vaccination 2 weeks prior; this patient reported symptoms after hearing about the other five events). The patients experienced hypoglycemic reactions (headache, light headed, nausea, cold sweat, heart racing, etc.). At least one case had documented low blood sugar (below 30) at a local Emergency Department. A vial of insulin for administration to diabetic students was stored in the same refrigerator in the school nurse's office as the FluLaval. The school system reported vaccinating

over 900 personnel from the same lot without other reactions. The incident was reported to the Local and State Health Departments and to the manufacturer. The local health department identified issues with storage of the FluLaval and insulin that may have contributed to a product mix-up. The manufacturer's investigation found no manufacturing issues with the involved lot and no similar cases from other locations receiving that lot. The manufacturer concluded that there was no quality issue and that inadvertent administration of insulin could not be ruled out. FDA's investigation and review of the findings of the manufacturer and other agencies involved agreed that vaccine and medication storage and handling practices were likely the primary factors contributing to these cases.

7.4 Periodic Benefit Risk Evaluation Report (PBRER)

The manufacturer's postmarket periodic safety report for FluLaval covering the period December 18, 2013 to December 17, 2014 was reviewed. No additional safety issues were identified.

8. LITERATURE REVIEW

A search of the US National Library of Medicine's PubMed.gov database for peer-reviewed literature published between August 16, 2013 and June 30, 2015 and using the search term "FluLaval", yielded no safety-related publications. One study by Roy-Ghanta et al, published in May 2014, assessed the immunogenicity of H1N1 pandemic vaccine in adults previously vaccinated with seasonal trivalent influenza vaccination.[9] This randomized, observer-blinded controlled study, conducted by GSK in 2010-2011, included 99 adults participants who received FluLaval followed by an H1N1 pandemic vaccine 4 months later. No safety concerns were observed.

9. INFLUENZA VACCINE SAFETY SURVEILLANCE ACTIVITIES

During each Northern Hemisphere influenza season, the FDA, CDC, and CMS collaborate and share information generated through several surveillance systems. In aggregate, these systems facilitate three key components of influenza vaccine safety surveillance: safety signal detection, surveillance for pre-specified adverse events of interest, and safety signal evaluation.

Safety Signal Detection

Co-managed by the CDC and FDA, VAERS is a spontaneous reporting system that allows healthcare providers, patients, vaccine manufacturers and others to report adverse events suspected to be associated with vaccines, including influenza vaccines.[10] VAERS can assess early indicators of a possible vaccine safety problem that present as new or unusual adverse events or patterns of reports.[11]

FDA and CDC medical officers and epidemiologists routinely review VAERS reports, and the VAERS contractor obtains follow-up information including relevant medical records for further evaluation of serious reported events (http://www.cdc.gov/vaccinesafety/Activities/vaers.html). Data mining algorithms complement review of VAERS records by identifying adverse events

that are disproportionally reported for a particular vaccine compared to other licensed vaccines .[12] New safety signals for influenza vaccines identified through VAERS can be evaluated in controlled epidemiologic studies for safety signal evaluation.

Surveillance for Pre-specified Adverse Events of Interest
Each season, both FDA and CDC use large electronic healthcare databases to monitor pre-specified adverse events of special interest.

Since 2009, FDA and the Centers for Medicare and Medicaid Services (CMS) have used healthcare claims data for U.S. Medicare beneficiaries to monitor hospitalizations and diagnosis codes for Guillain-Barré Syndrome (GBS) after live and inactivated influenza vaccines. This prospective active adverse event surveillance provides timely GBS rate-based comparisons among a population exceeding 42 million individuals.[13]

Established in 1990, the Vaccine Safety Datalink (VSD) is a collaborative project between the CDC and 9 health care organizations. Weekly VSD Rapid Cycle Analysis enables rate-based comparisons among a population exceeding 9 million individuals (http://www.cdc.gov/vaccinesafety/Activities/vsd.html). This surveillance includes approximately 4-5 adverse events each flu season and involves live and inactivated vaccines.[14,15]

Safety Signal Evaluation

In addition to seasonal surveillance for pre-specified adverse events of interest, VSD[16] and CMS[17] databases have been used to evaluate safety signals for influenza vaccines. The Post-Licensure Rapid Immunization Safety Monitoring system (PRISM), a component of the FDA's Sentinel Initiative dedicated to vaccines, has also been used to evaluate safety signals for influenza vaccines.[18] The PRISM system uses the FDA's Sentinel Distributed Database which includes a population exceeding 100 million. (http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm397611.htm). If warranted, FDA and/or CDC can use such large data sources to evaluate potential safety signals through controlled epidemiologic studies. These studies can determine if an observed safety signal reflects a true association between the influenza vaccine and the adverse event, and if so, ascertain the magnitude of the association.

10. CONCLUSION

This comprehensive postmarketing pediatric safety review of passive surveillance adverse event reports, periodic safety reports, and the published literature for FluLaval does not indicate any new safety concerns. There were few reports of adverse events received during the time period of this review, compared to the number of patients estimated to have used the product. Most adverse event reports in pediatric patients were non-serious and were consistent with the known safety profile of influenza vaccines. The cluster of hypoglycemia-related events in adult recipients was likely related to accidental administration of insulin instead of influenza vaccine stemming from storage and handling practices and not an effect of the vaccine. No other unusual frequency, clusters, or other trends for adverse events were identified. The product label

adequately reflects the known safety profile for FluLaval.

11. RECOMMENDATIONS

FDA recommends continued routine safety monitoring of FluLaval. No further regulatory action is indicated at this time.

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