



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

MEMORANDUM

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From: Craig Zinderman, MD, MPH
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Subject: Pediatric Safety and Utilization Review for the
Pediatric Advisory Committee (PAC) Meeting

Sponsor: ID Biomedical Corporation of Quebec

Product: FluLaval Quadrivalent (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 Trivalent vs. Quadrivalent Formulations of Seasonal Influenza Vaccines

Trivalent (three-strain) influenza vaccines protect against the strains expected to be predominant in humans in a given year - two subtype A virus strains and a type B strain. Two influenza B virus lineage strains circulate to varying degrees each year making it difficult to predict which one will predominate in a particular influenza season. Quadrivalent (four-strain) influenza vaccine formulations are designed to protect against both influenza B strains, providing additional coverage.

1.2 Regulatory History

FluLaval is a seasonal, inactivated, split-virion, trivalent influenza vaccine (TIV) that has been licensed and distributed in the U.S. since 2006. FluLaval is manufactured by ID Biomedical Corporation of Quebec (a subsidiary of GlaxoSmithKline Biologicals (GSK)) and 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 currently approved for use in persons 3 years of age and older. FluLaval TIV, which is also marketed outside of the United States as Fluviral or GripLaval (hereafter referred to as FluLaval for the purposes of this review), was first licensed December 18, 1992 in Canada, and it is marketed in 16 countries (as of June 30, 2012).

1.2.2 FluLaval Quadrivalent

FluLaval Quadrivalent (FluLaval QIV) is an inactivated quadrivalent influenza virus vaccine indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. FluLaval QIV was approved in the US on August 15, 2013 for use in persons 3 years of age and older.

The processes for manufacturing this quadrivalent influenza vaccine are similar to those for the FluLaval (trivalent) vaccine, aside from the addition of a B strain. The hemagglutinin (HA) antigen concentration per 0.5 mL dose is 15 µg HA per strain, the same as for the trivalent product. Thus, each dose of QIV contains a total of 60 µg HA, rather than 45 µg HA in the trivalent formulation.

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

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 including 18 months following the approval of FluLaval QIV 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 15, 2013 approval of FluLaval QIV in individuals 3 years and older. This review covers the period from August 15, 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 QIV. 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 QIV submitted August 15, 2013 - June 30, 2015.

3.2 Manufacturer's Submissions

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

3.3 FDA Documents

- FluLaval QIV Approval Letter, dated August 15, 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 6.8 million doses of FluLaval QIV were distributed in the US from August 15, 2013 to 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 6,260,000 doses were distributed worldwide from product launch through 10/31/2014.

6. PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

This section describes GlaxoSmithKline's pharmacovigilance plan (PVP) for FluLaval QIV. 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 QIV from pre-licensure clinical studies or from post-market safety monitoring.

Potential risks included by the sponsor for FluLaval QIV are the same as those for FluLaval TIV and 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 market⁴, although a subsequent, well-designed epidemiological study did not show an association with other inactivated influenza vaccines and the development of Bell's palsy.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 QIV.

FDA has not required any postmarketing study of FluLaval QIV in the approved age range for any safety reason. The sponsor committed to conduct a pregnancy registry upon approval which is ongoing and has not identified any safety issues to date. The pregnancy registry is to be conducted for five years; following which the manufacturer will submit a final study report.

The pregnancy registry was subsequently 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 QIV 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. As of 12/17/14 (data lock point of the sponsor's most recent PBRER), 10 pregnancies in the US were prospectively reported to the registry with exposure to FluLaval QIV: 3 were lost to follow-up, 3 are ongoing, and the status of the remaining 4 was reported as unknown.

There are no other completed or outstanding postmarketing safety study commitments or requirements to address safety concerns for FluLaval QIV. Under the Pediatric Research Equity Act (PREA) the sponsor is required to conduct a study to evaluate the safety and immunogenicity of FluLaval QIV 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.

7. ADVERSE EVENT REVIEW

7.1 Methods

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event reports following use of FluLaval QIV between August 15, 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.

7.2 Results

The results of the VAERS search of adverse events for FluLaval QIV 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.

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	0	0	0	0	0	0	2	0	2	2	0	2
3-17	1	0	1	0	0	0	15	0	15	16	0	16
≥18	9	0	9	2	0	2	90	0	90	102	0	102
Unknown	0	0	0	0	0	0	7	0	7	7	0	7
Total	10*	0	10*	2	0	2	114	1	114	126	0	126

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

Table 1 summarizes the 126 adverse event reports submitted during the review period to VAERS for FluLaval QIV, overall and by age. A total of 18 pediatric reports, including 1 non-fatal serious report, involved children 0 through 17 years of age.

7.2.1 Deaths

No pediatric deaths were reported following vaccination with FluLaval QIV.

Adult deaths

Two adult deaths were reported in the review period. An 87 year old female received FluLaval QIV on 11/7/2014 and subsequently died on (b) (6). The death certificate indicated that cause of death was heart failure. In the second case, a 77 year old male received FluLaval on 11/7/2014 and died on (b) (6). The death certificate indicated cause of death as Parkinson's disease.

7.2.2. Non-fatal serious reports

A single Non-fatal Serious Adverse Event was reported among Children 0-17 years of age.

A 4 year old male received FluLaval QIV along with DTaP/IPV, MMR, and Varicella vaccines on 2/6/14. “Shortly after” vaccination, the patient developed mild cough, nasal congestion, and bilateral eye swelling. His physician diagnosed his symptoms as allergic reaction and sent him to a local Emergency Department (ED). At the ED, he was observed to have no respiratory distress or wheezing. He was treated with steroids and epinephrine and discharged home.

The 9 adult non-fatal serious reports included 2 reports of injection site reactions. No other type of adverse event occurred more than once among the remaining reports.

7.2.3 Non-serious Reports

During the reporting period there were 114 non-serious adverse events, 17 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 reactions (including injection site erythema, swelling and/or pain (N=4), rash/ urticaria (N=3), and syncope (N=2). The pediatric non-serious reports also included five events of inadvertent administrations without associated adverse events (e.g., wrong vaccine, child younger than indicated age range).

7.3 Data Mining

Data mining was conducted using Empirica Signal software version 7.2 to evaluate whether any events following use of FluLaval QIV were disproportionately 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 QIV 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) or the 2014-2015 influenza vaccination season (via query run with data available through 9/2/2015).

7.4 Periodic Benefit Risk Evaluation Report (PBRER)

The manufacturer’s postmarket periodic safety reports for FluLaval QIV covering the period December 18, 2013 to December 17, 2014 were 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 15, 2013 and June 30, 2015 and using the search term “FluLaval”, yielded no safety-related publications for FluLaval QIV.

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.⁹ VAERS can assess early indicators of a possible vaccine safety problem that present as new or unusual adverse events or patterns of reports.¹⁰

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 disproportionately reported for a particular vaccine compared to other licensed vaccines.¹¹ 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.¹²

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.^{13,14}

Safety Signal Evaluation

In addition to seasonal surveillance for pre-specified adverse events of interest, VSD¹⁵ and CMS¹⁶ 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.¹⁷ 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 QIV 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. No unusual frequency, clusters, or other trends for adverse events were identified. The product label adequately reflects the known safety profile for FluLaval QIV.

11. RECOMMENDATIONS

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

¹ CDC. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP) — United States, 2014–15 Influenza Season. Groshkopf LA, Olsen SJ, Skolow LZ, Bresee JS, Cox NJ, Broder KR, Karron RA, Walter EB. *Morbidity and Mortality Weekly Report*. August 15, 2014. 63(32):691-697.

² Armstrong PK, Dowse GK, Effler PV, et al. Epidemiological study of severe febrile reactions in young children in Western Australia caused by a 2010 trivalent inactivated influenza vaccine. *BMJ* 2011;1:e000016.

³ Therapeutic Goods Administration. Overview of vaccine regulation and safety monitoring and investigation into adverse events following 2010 seasonal influenza vaccination in young children. Canberra: TGA, 2010 [retrieved 2011 November 15]. Available at the TGS web site: tga.gov.

⁴ Mutsch M, Zhou W, Rhodes P, et al. Use of the inactivated intranasal influenza vaccine and the risk of Bell's palsy in Switzerland. *N Engl J Med* 2004;350:896-903.

⁵ Stowe J, Andrews N, Wise L, et al. Bell's palsy and parenteral inactivated influenza vaccine. *Human Vaccines* 2006;2:110-2.

⁶ Schonberger LB, Bregman DJ, Sullican-Bloyai JZ, et al. Guillain-Barré syndrome following vaccination in the National Influenza Immunization Program, United States, 1976-1977. *Am J Epidemiol* 1979;110:105-23.

⁷ Stowe J, Andrews N, Wise L, Miller E. Investigation of the temporal association of Guillain-Barre syndrome with influenza vaccine and influenza-like illness using the United Kingdom General Practice Research Database. *Am J Epidemiol*. 2009 Feb 1;169(3):382-8.

⁸ IOM (Institute of Medicine). 2012. *Adverse effects of vaccines: Evidence and causality*. Washington, DC: The National Academies Press. http://www.nap.edu/catalog.php?record_id=13164

⁹ Varricchio F, Iskander J, Destefano F, Ball R, Pless R, Braun MM, Chen RT. Understanding vaccine safety information from the Vaccine Adverse Event Reporting System. *Pediatric Infectious Disease* 2004 Apr;23(4):287-94.

¹⁰ Salmon DA, Akhtar A, Mergler MJ, Vannice KS, Izurieta H, Ball R, Lee GM, Vellozzi C, Garman P, Cunningham F, Gellin B, Koh H, Lurie N; H1N1 Working Group of Federal Immunization Safety Task

Force. Influenza Vaccination Program Immunization-Safety Monitoring Systems for the 2009 H1N1 Monovalent Influenza Vaccination Program. *Pediatrics*. 2011 May;127 Suppl 1:S78-86.

¹¹ Martin D, Menschik D, Bryant-Genevier M, Ball R. Data mining for prospective early detection of safety signals in the Vaccine Adverse Event Reporting System (VAERS): a case study of febrile seizures after a 2010-2011 seasonal influenza virus vaccine. *Drug Saf*. 2013 Jul;36(7):547-56.

¹² Burwen DR, Sandhu SK, MaCurdy TE, Kelman JA, Gibbs JM, Garcia B, Markatou M, Forshee RA, Izurieta HS, Ball R; Safety Surveillance Working Group. Surveillance for Guillain-Barré syndrome after influenza vaccination among the Medicare population, 2009-2010. *Am J Public Health*. 2012 Oct;102(10):1921-7.

¹³ McNeil MM1, Gee J2, Weintraub ES2, Belongia EA3, Lee GM4, Glanz JM5, Nordin JD6, Klein NP7, Baxter R7, Naleway AL8, Jackson LA9, Omer SB10, Jacobsen SJ11, DeStefano F2. The Vaccine Safety Datalink: successes and challenges monitoring vaccine safety. *Vaccine*. 2014 Sep 22;32(42):5390-8.

¹⁴ Kawai et al. Absence of associations between influenza vaccines and increased risks of seizures, Guillain-Barré syndrome, encephalitis, or anaphylaxis in the 2012-2013 season. *Pharmacoepidemiol Drug Saf*. 2014 May;23(5):548-53.

¹⁵ Tse et al. Signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010-2011. *Vaccine*. 2012 Mar 2;30(11):2024-31.

¹⁶ Polakowski LL, Sandhu SK, Martin DB, Ball R, Macurdy TE, Franks RL, Gibbs JM, Kropp GF, Avagyan A, Kelman JA, Worrall CM, Sun G, Kliman RE, Burwen DR. Chart-confirmed Guillain-Barré syndrome after 2009 H1N1 influenza vaccination among the Medicare population, 2009-2010. *Am J Epidemiol*. 2013 Sep 15;178(6):962-73.

¹⁷ PRISM Update: FDA Postlicensure Rapid Immunization Safety Monitoring (PRISM) study demonstrates no statistically significant association between Trivalent Inactivated Influenza Vaccine and Febrile Seizures in Children during the 2010-2011 influenza season. Updated May 15, 2014. <http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm397611.htm>