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

MEMORANDUM

To: Craig Zinderman, MD, MPH
Associate Director for Medical Policy
Office of Biostatistics and Epidemiology (OBE)
Center for Biologics Evaluation and Research (CBER)

Through: Meghna Alimchandani, MD
Deputy Director, Division of Epidemiology (DE), OBE, CBER

From: Jane Baumblatt, MD
Medical Officer Team Lead, Analytic Epidemiology Branch
DE, OBE, CBER

Subject: Safety and Utilization Review for the Pediatric Advisory Committee

Applicant: ID Biomedical Corporation of Quebec [Subsidiary of GlaxoSmithKline Biologicals (GSK)]

Product: FluLaval (influenza vaccine)

STN: 125163/597

Indication: FluLaval is an inactivated vaccine 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 aged 6 months and older.

Meeting Date: Pediatric Advisory Committee Meeting, September 2020

Contents

1 INTRODUCTION

1.1 Objective

This memorandum for the Pediatric Advisory Committee (PAC) presents a comprehensive review of the postmarketing pediatric safety covering a period including 18 months following the approval in accordance with Section 505B (i) (1) of the Food and Drug Cosmetic Act [21 U.S.C. §355c]. The trigger for this pediatric postmarketing safety review was the approval of BLA supplement 125163/405 on November 18, 2016 to extend the age range for use of FluLaval to include children 6 to 35 months of age.

This memorandum documents the Food and Drug Administration's (FDA's) complete evaluation, including review of adverse event (AE) reports in passive surveillance data, periodic safety reports from the manufacturer, data mining, and a review of the published literature.

1.2 Product Description

FluLaval is an inactivated vaccine 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 aged 6 months and older[1]

FluLaval is a trivalent, split virion, seasonal influenza vaccine containing the purified outer membrane protein hemagglutinin (HA) from each of three influenza virus strains The HA antigens are derived from viruses propagated in embryonated chicken eggs. Each dose contains 45 micrograms (mcg) HA in the recommended ratio of 15mcg HA of each of the 3 influenza strains. This vaccine is presented as a suspension for intramuscular injection supplied in 0.5mL single-dose, prefilled syringes and 5mL multi-dose vials. The prefilled syringe is formulated without preservatives and does not contain thimerosal. Each 0.5mL dose from the multi-dose vial contains 50mcg thimerosal (< 25 mcg mercury); thimerosal, a mercury derivative, is added as a preservative.

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.[2]

[1] FluLaval U.S. package insert; updated 11/2016

[2] Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2019–20 Influenza Season. Lisa A. Grohskopf, MD; Elif Alyanak; Karen R. Broder; Emmanuel B. Walter; Alicia M. Fry; Daniel B. Jernigan. Morbidity and Mortality Weekly Report. August 23, 2019 / 68(3);1–21.Available at https://www.cdc.gov/mmwr/volumes/68/rr/rr6803a1.htm

1.3 Regulatory History

- December 18, 1992: Approval of FluLaval in Canada.
  [Note: FluLaval is marketed outside of the U.S. as Fluviral or GripLaval.]

- October 5, 2006: FDA initial approval of STN 125163/0 for use of FluLaval in adults ≥ 18 years under accelerated approval regulations, 21 CFR 601.41

- August 16, 2013: FDA approval of STN 125163/254 for use of FluLaval in persons ≥ 3 years
  - This approval triggered a prior presentation to the 2016 PAC for the review period August 16, 2013 – June 30, 2015
- November 18, 2016: FDA granted approval of STN 125163/405 for use of FluLaval in persons 6 to 35 months
  - This approval is the trigger for the presentation to the 2020 PAC for the review period November 18, 2016 – February 29, 2020

2 MATERIALS REVIEWED

- Vaccine Adverse Events Reporting System (VAERS)
  - VAERS reports for FluLaval during November 18, 2016 to February 29, 2020 (PAC review period)
- Manufacturer's Submissions
  - FluLaval U.S. package insert; updated 11/2016
  - Applicant response to information request regarding dose distribution data, received 4/30/2020
  - Pharmacovigilance Plan, version 2, dated September 30, 2014
  - Periodic safety reports
- FDA Documents
  - STN 125163/405 FluLaval and FluLaval Quadrivalent Approval Letter, dated November 18, 2016
  - STN 125163/405 OBE/DE Pharmacovigilance Plan Review Memorandum
- Publications (see Literature Search in Section 7)

3 LABEL CHANGES IN REVIEW PERIOD

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

4 PRODUCT UTILIZATION DATA

GSK provided distribution data for the US and worldwide (i.e., outside the U.S.) for time intervals November 18, 2016 to February 29, 2020:

Total doses distributed in the US was 16,000 doses. FluLaval TIV was no longer distributed after FDA granted approval for use of FluLaval QIV in persons 6 to 35 months in November 2016.

Period	2016*	2017	2018	2019	2020**	Total
Doses (thousands)	16	0	0	0	0	16

*November and December only
**January and February

Total doses distributed worldwide was 7,412,000 doses.

Period	2016*	2017	2018	2019	2020**	Total
Doses (thousands)	42	4,202	3,530	2,274	895	7,412

*November and December only
**January and February

The sponsor was not able to provide data on proportion of doses distributed to pediatric and adult patients. Note that the number of doses distributed is an estimate of the number of patients vaccinated because doses may have been distributed without being administered to patients or patients may have received more than one dose.

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan

The manufacturer's current Pharmacovigilance Plan (PVP), version 2, dated September 30, 2014, lists the following important identified and potential risks, and missing information for FluLaval (see Table 1).

Table 1: FluLaval Safety Concerns

Important Identified Risks
None
Important Potential Risks
Anaphylaxis
Febrile seizure
Bell's Palsy
Guillain-Barré Syndrome
Injection site hemorrhage in individuals with thrombocytopenia or any other coagulation disorder
Narcolepsy
Missing Information
Use during pregnancy
Use during lactation

Anaphylaxis: Allergic reactions including anaphylaxis have been reported with FluLaval and is labeled in section *6.2 Postmarketing Experience*. FluLaval is contraindicated in

anyone with a history of severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine, including egg protein, or following a previous dose of any influenza vaccine (labeled in section 4 *Contraindications*).

Febrile seizure: Febrile seizures were detected in young children in Western Australia in association with another seasonal vaccine in 2010.[3, 4]

Bell's palsy: 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[5]. A subsequent, well-designed epidemiological study did not show an association with other inactivated influenza vaccines and the development of Bell's palsy.[6]

Guillain-Barré Syndrome: Guillain-Barré Syndrome (GBS) is labeled in section 5 *Warnings and Precautions*. GBS was associated with use of an A/New Jersey 1976 influenza vaccine in anticipation of a swine influenza epidemic,[7] and is routinely listed in the label of influenza vaccines.

Narcolepsy: 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.

The identified and potential risks listed in Table 1 are common to this product class and will be monitored with routine safety surveillance, including review of adverse event reports submitted to FDA, manufacturer submitted periodic safety reports, published literature, and data mining. There are no postmarketing requirement (PMR) safety-related studies under FDAAA or Risk Evaluation and Mitigation Strategy (REMS) for FluLaval. The sponsor is also conducting a pregnancy registry study (please see section 5.2).

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[3] 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.
[4] Therapeutic Goods Administration. Seasonal flu vaccine: Overview of vaccine regulation and safety monitoring and investigation into adverse events following 2010 seasonal influenza vaccination in young children. Available: https://www.tga.gov.au/alert/seasonal-flu-vaccine-overview-vaccine-regulation-and-safety-monitoring-and-investigation-adverse-events-following-2010-seasonal-influenza-vaccination-young-children
[5] 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.
[6] Stowe J, Andrews N, Wise L, et al. Bell's palsy and parenteral inactivated influenza vaccine. Human Vaccines 2006;2:110-2.
[7] 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.

5.2 Postmarketing Studies

Pediatric postmarketing requirement (PMR) under the Pediatric Research Equity Act (PREA): Applicant has fulfilled the pediatric study requirement for all relevant pediatric age groups.

Pregnancy registry: Applicant is conducting the following combined pregnancy registry for GSK inactivated influenza vaccines (FluLaval, FluLaval Quadrivalent, Fluarix, Fluarix Quadrivalent):

- An exploratory prospective, cohort study (Protocol EPI-FLU-039) to detect and describe abnormal pregnancy outcomes in women intentionally or unintentionally vaccinated with Fluarix or Fluarix Quadrivalent or FluLaval or FluLaval Quadrivalent during pregnancy or within 28 days preceding conception.
- Status: Ongoing. [Final study report submission date: May 31, 2020]

6 ADVERSE EVENT REVIEW

6.1 Methods

The Vaccine Adverse Event Reporting System (VAERS) was queried for adverse event reports following use of FluLaval between November 18, 2016 and February 29, 2020. VAERS stores postmarketing adverse events and medication errors submitted to FDA and CDC for all approved vaccines. These reports originate from a variety of sources, including healthcare providers, consumers, and manufacturers. 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. Reports in VAERS may not be medically confirmed and are not verified by FDA. FDA does not receive reports for every adverse event or medication error that occurs with a vaccine. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Also, there is no certainty that the reported event was actually due to the vaccine.

6.2 Results

The results of the VAERS search of AE reports for FluLaval during the PAC review period are listed in Table 2 below. There were 3 US and 10 foreign reports for review period November 18, 2016 to February 29, 2020.

Table 2: FluLaval VAERS reports during November 18, 2016 – February 29, 2020

Age	Serious non-fatal, US	Serious Non-fatal, Foreign	Deaths, US	Deaths, Foreign	Non-Serious, US	Non-Serious, Foreign	Total, US	Total, Foreign
<18 years	0	1	0	0	0	0	0	1
≥18 years	1	3	0	0	1	0	2	3
Unknown	0	6	0	0	1	0	1	6

Age	Serious non-fatal, US	Serious Non-fatal, Foreign	Deaths, US	Deaths, Foreign	Non-Serious, US	Non-Serious, Foreign	Total, US	Total, Foreign
All ages	1	10	0	0	2	0	3	10

Note: Serious non-fatal adverse events include life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, or significant disability, and otherwise medically important conditions (OMIC).

6.2.1 Deaths

No deaths were reported following FluLaval during the PAC review period.

6.2.2 Serious Non-fatal Reports

During the PAC review period, there were 11 serious non-fatal reports, including 1 pediatric report. Age was unknown for 6 serious non-fatal reports.

Pediatric serious non-fatal report:
This was a report of cellulitis in a 3-year-old male patient post receipt of FluLaval and Quadracel. Medical history and concomitant medications were not reported.
On an unspecified date post-vaccination, the patient developed injection site erythema, induration and peripheral extremity swelling, and was diagnosed with cellulitis that lasted for nine days. At the time of the report, the cellulitis had resolved.

Adult serious non-fatal reports
There were 4 serious non-fatal reports involving adults. The most common Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) among serious reports are displayed in Table 3. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 3: Most frequently reported PTs for serious non-fatal reports

Preferred Term (PT)	**Number of Serious Reports**	**Label* Status** *Label dated 11/2016 (Label Sections)
Asthenia	2	Labeled (6.2)
Erythema	2	Labeled (6.1)
Insomnia	2	Labeled (6.2)

6.1 Clinical Trials Experience; 6.2: Postmarketing Experience
Note: PTs occurring with a frequency >1 report are shown in above table.

Reviewer comments: *All three most common PTs are labeled events for this product.*

6.2.3 Non-serious Reports

During the reporting period, there were 2 non-serious reports. One non-serious report involved a 42-year-old female who experienced shaking, profuse sweating, shallow breathing and transient left leg paralysis a few hours post receipt of FluLaval. The patient was seen in the ER, a workup was negative, and symptoms subsequently resolved. The second non-serious report involving a patient of unknown age who on an

unknown date after receiving FluLaval, experienced influenza-like symptoms, chills, headache and malaise. The outcome of the events was unknown.

6.3 Data mining

Data mining was performed to evaluate whether any reported events following the use of FluLaval were disproportionally reported compared to other vaccines in the VAERS database. The background database contains VAERS reports since 1990. Disproportionality alerts do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation. A query of Empirica Signals Management with the US VAERS Vac Name run with a data lock date of April 28, 2020 for INFLUENZA (SEASONAL) (FLULAVAL) did not identify any PTs with a disproportional reporting alert (EB05>2; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean).

6.4 Periodic safety reports

The manufacturer's postmarketing periodic safety reports for FluLaval were reviewed. The AEs reported were consistent with those seen in VAERS. No additional safety issues were identified, and no actions were taken by the sponsor for safety reasons.

7 LITERATURE REVIEW

A search of the US National Library of Medicine's PubMed.gov database on April 23, 2020 for peer-reviewed literature, with the search term "FluLaval" and "safety" limited by human species, and dates from PAC trigger (November 18, 2016) to date of search (April 23, 2020), retrieved no publications pertaining to safety.

8 CONCLUSION

This postmarketing pediatric safety review was triggered by the November 18, 2016 approval for use of FluLaval in persons 6 to 35 months. Review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for FluLaval does not indicate any new safety concerns. There were no deaths. There were very few VAERS reports during the review period. No unusual frequency, clusters, or other trends for adverse events were identified that would suggest a new safety concern.

9 RECOMMENDATIONS

FDA recommends continued routine safety monitoring of FluLaval TIV.