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)
From:	Meghna Alimchandani, MD Deputy Director, Division of Epidemiology (DE), OBE, CBER
Subject:	Safety and Utilization Review for the Pediatric Advisory Committee
Applicant:	ID Biomedical Corporation of Quebec (GlaxoSmithKline)
Product:	Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted
STN:	125419
Indication:	For active immunization for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine. It is approved for use in persons 6 months and older at increased risk of exposure to the influenza A virus H5N1 subtype contained in the vaccine.
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 September 9, 2016 approval of BLA supplement 125419/39 for Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted to extend the age range for use to include persons 6 months through 17 years of age at increased risk of exposure to the influenza A virus H5N1 subtype contained in the vaccine. While there is no approved trade name for Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted, hereafter in this memo the vaccine will be referred to as Q-Pan H5N1 vaccine.

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

Q-Pan H5N1 vaccine is indicated for active immunization for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine. It is approved for use in persons 6 months and older. Q-Pan H5N1 is included in the U.S. Strategic National Stockpile as part of the national strategy for pandemic influenza preparedness. The stockpiled vaccine will be distributed by the US government in the event of an H5N1 pandemic.

Q-Pan H5N1 is a non-infectious, 2-component monovalent, AS03-adjuvanted vaccine. The vaccine is supplied as a vial of inactivated, split-virion, A/H5N1 influenza antigen suspension and a vial of AS03 adjuvant emulsion that must be combined prior to administration by intramuscular injection. The adult dose is 0.5 mL and the pediatric dose is 0.25 mL, with a dosing regimen of two doses administered 21 days apart. The A/H5N1 antigen suspension is manufactured according to the same process as that used to produce the antigens contained in FluLaval and FluLaval Quadrivalent, which are unadjuvanted seasonal influenza vaccines licensed in U.S.

1.3 Regulatory History

- April 3, 2011: European Medicines Agency (EMA) granted marketing authorization for Q-Pan H5N1 vaccine under the trade name Pumarix.
- November 22, 2013: FDA initial approval of Q-Pan H5N1 vaccine (STN 125419/0) for use in adults ≥18 years.
- September 9, 2016: FDA approval of supplement (STN 125419/39) to extend the age range to include persons 6 months through 17 years.

2 MATERIALS REVIEWED

- Vaccine Adverse Events Reporting System (VAERS) reports
- Manufacturer submissions
    - Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted U.S. package insert, dated September 2016
    - Q-Pan H5N1 vaccine Pharmacovigilance Plan, Version 5, dated May 2016
    - Periodic safety reports
- FDA Documents
    - Approval Letter for STN 125419/39, dated September 9, 2016
    - Approval Letter for STN 125419/0, dated November 22, 2013
- Publications (see Literature Search in Section 7)

3 LABEL CHANGES IN REVIEW PERIOD

There have been no label changes related to safety concerns for Q-Pan H5N1 vaccine during September 9, 2016 to February 29, 2020 (PAC review period).

4 PRODUCT UTILIZATION DATA

Q-Pan H5N1 vaccine is held in the U.S. Strategic National Stockpile and will be distributed by the US government in the event of an H5N1 influenza virus pandemic. Q-Pan H5N1 vaccine has never been marketed in the US.

The most recent Periodic Benefit Risk Evaluation Report (PBRER) for the reporting period of May 20, 2018 through May 19, 2019 (submitted under STN 125419/94), indicates that no doses of Q-Pan H5N1 vaccine have been administered.

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan

The manufacturer's current Pharmacovigilance Plan (PVP), version 5, dated May 2016, did not list any important identified or potential risks. However, the sponsor, identified the following events as "potential safety concerns," because they are associated with influenza vaccines in general or were observed with postmarketing use of non-U.S. licensed AS03 adjuvanted H1N1 vaccines in 2009: Anaphylaxis; increased concentration of hepatic enzymes; Bell's palsy; convulsion; demyelinating disorders; encephalitis; Guillain Barré syndrome; narcolepsy; neuritis; potential immune-mediated diseases (pIMDs); vasculitis; vaccination failure. The following medication error or product quality events were also considered by the sponsor to be potential safety concerns: medical errors/misidentification of vaccine; contamination of multiple-dose vials; coring of the rubber stopper on the antigen vial.

There are theoretical concerns of potential autoimmunity associated with Q-Pan H5N1 and other vaccines containing certain adjuvants, such as AS03. There is no postmarketing experience following administration of Q-Pan H5N1 vaccine. Section 6.2

Postmarketing Experience includes events (anaphylaxis, autoimmune hepatitis, febrile convulsions, Guillain Barré syndrome, narcolepsy) reported following the use of non-U.S. licensed AS03-adjuvanted H1N1 influenza vaccines (Pandemrix[1] and Arepanrix[2]), also manufactured by GSK, and distributed during the Influenza A 2009 H1N1 pandemic. Guillain Barré syndrome (GBS) is also labeled under 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 and is routinely listed in the label of influenza vaccines.[3]

Narcolepsy: As per the sponsor, "no reports of narcolepsy have been received by GSK from participants in clinical trials of AS03-adjuvanted vaccines." Narcolepsy is included in the Q-Pan H5N1 vaccine label, section 6.2 *Postmarketing Experience*, based on spontaneous postmarketing AE reports for non-U.S. licensed AS03-adjuvanted H1N1 influenza vaccines, as well as epidemiology studies. The label includes the following information on narcolepsy studies:

> *Epidemiological studies[4, 5, 6, 7, 8, 9, 10] in several European countries evaluated a potential association between an influenza vaccine containing AS03 adjuvant, Influenza vaccine (A/California/7/2009 H1N1), manufactured by GlaxoSmithKline in Dresden, Germany, and narcolepsy. Some published studies reported a 2.9- to 14.2-fold increase in the risk of narcolepsy, with or without cataplexy, among vaccinated children and adolescents (younger than 20 years), and a 2.2- to 5.5-fold increase among vaccinated adults aged 20 years and older, compared with individuals of the same age group who did not receive this H1N1 vaccine. Approximately 3 to 8 additional cases of narcolepsy per 100,000 vaccinated children/adolescents and approximately 1 additional case per 100,000 vaccinated adults were estimated to occur based on data from some of these studies. No increase in the risk of narcolepsy was reported in some studies. The relevance of these findings on narcolepsy to the United States population or to the Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted is unknown.*

[1] Pandemrix was manufactured by GSK in Dresden, Germany using a manufacturing process that is different than that used for Q-Pan H5N1.
[2] Arepanrix was manufactured by GSK in Quebec, Canada using the same manufacturing process that is used for Q-Pan H5N1.
[3] 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.
[4] European Centre for Disease Prevention and Control. Narcolepsy in association with pandemic influenza vaccination (a multi-country European epidemiological investigation) Stockholm: ECDC; September 2012, Stockholm, Sweden, ISBN 978-92-9193-388-4. (VAESCO report).
[5] Nohynek H, et al. AS03 adjuvanted AH1N1 vaccine associated with an abrupt increase in the incidence of childhood narcolepsy in Finland, PLoS One. 2012;7(3): e33536. Epub 2012 Mar 28.
[6] Medical Products Agency (MPA) Sweden. Occurrence of narcolepsy with cataplexy among children and adolescents in relation to the H1N1 pandemic and Pandemrix vaccinations – Results of a case inventory study by the MPA in Sweden during 2009–2010. June 30, 2011.
[7] Reilly J. Final Report of National Narcolepsy Study Steering Committee, Investigation of an increase in the incidence of narcolepsy in children and adolescents in 2009 and 2010. April 19, 2012.
[8] Dauvilliers Y et al. Narcoflu-VF study group. Increased risk of narcolepsy in children and adults after pandemic H1N1 vaccination in France. Brain. 2013:136;2486-2496.
[9] Jokinen J, et al. Association between the pandemic vaccine and narcolepsy in adults - Cohort study based on confirmed register data. 2013
[10] Persson I. et al. Risks of neurological and immune-related diseases, including narcolepsy, after vaccination with Pandemrix: a population- and registry-based cohort study with over 2 years of follow-up. J Intern Med.2013; Oct 17.

Missing information for Q-Pan H5N1 vaccine includes data in children aged younger than 6 months; data in pregnant women; individuals with clinically severe underlying medical conditions; and immunocompromised individuals.

The safety concerns for Q-Pan H5N1 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. Additionally, the sponsor agreed to conduct enhanced pharmacovigilance for certain adverse events of special interest and will submit 15-day reports for all (serious or nonserious) events of narcolepsy (with or without cataplexy) and autoimmune hepatitis to VAERS. To effectively monitor the safety profile of Q-Pan H5N1 vaccine during an officially declared H5N1 pandemic, the sponsor will submit periodic safety reports at monthly intervals, accompanied by a summary of vaccine distribution.

There are no safety-related postmarketing requirement (PMR) studies under Food and Drug Administration Amendments Act (FDAAA) or Risk Evaluation and Mitigation Strategy (REMS) for Q-Pan H5N1 vaccine. The sponsor will conduct a pregnancy registry as a postmarketing commitment (PMC) to prospectively collect data on the safety of the Q-Pan H5N1 vaccine during pregnancy in the event of H5N1 influenza virus pandemic (please see section 5.2).

5.2 Postmarketing Studies

Pregnancy registry postmarketing commitment (PMC)[11]

To establish a pregnancy registry in the U.S. that prospectively collects data on an actively recruited cohort to study the safety of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted during pregnancy. A concept protocol for this pregnancy registry will be finalized once the vaccine is distributed for an officially-declared H5N1 influenza virus pandemic and its circumstances of use are determined.

Concept Protocol Submission: June 30, 2014
Final Protocol Submission: 60 days after notification by the FDA to finalize the protocol and initiate the registry
Study Completion Date: 24 months after initiation of the registry
Final Report Submission: 12 months after completion of data collection

Pediatric postmarketing requirements (PMR) under the Pediatric Research Equity Act[12]

- The sponsor has completed the study to evaluate the safety and immunogenicity of Q-Pan H5N1 vaccine in children 6 months to <18 years of age.

  [Note: This was the basis for approval of STN 125419/39 to extend the age range for use to include persons 6 months to < 18years; the trigger for this PAC review.]

[11] Approval Letter for STN 125419/0, dated November 22, 2013
[12] Approval Letter for STN 125419/39, dated September 9, 2016

- The sponsor will conduct a study to evaluate the safety and immunogenicity of Q-Pan H5N1 vaccine in infants < 6 months of age, according to the following schedule:

  Final Protocol Submission: 2 weeks after notification by the FDA to finalize the protocol in the event of an imminent H5N1 influenza virus pandemic (human to human H5N1 transmission)
  Study Completion Date: 16 months after initiation of the study
  Final Report Submission: 4 months after completion of data collection

  Status: Deferred pediatric study

6 ADVERSE EVENT REVIEW

6.1 Methods

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

Q-Pan H5N1 is being stockpiled for distribution by the US government in the event of an H5N1 pandemic. No doses of Q-Pan H5N1 have been distributed to the population, and there are no AE reports submitted to VAERS.

6.3 Periodic safety reports

The manufacturer's postmarketing periodic safety reports for Q-Pan H5N1 were reviewed. No new 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 May 1, 2020, for peer-reviewed literature, with the search term "H5N1 vaccine" and "safety" limited by human species, and dates from PAC trigger (September 9, 2016) to date of search (May 1, 2020), retrieved 16 publications. Titles and abstracts were reviewed and after excluding 12 publications that were not directly relevant to H5N1 vaccine, the remaining 4 publications are summarized below. No new safety concerns for Q-Pan H5N1 were identified in the review of these publications.

Publication	Authors' Safety Conclusion
Standaert B et al. Usability of daily SF36 questionnaires to capture the QALD variation experienced after vaccination with AS03A-adjuvanted monovalent influenza A (H5N1) vaccine in a safety and tolerability study. Health Qual Life Outcomes. 2019 May 6;17(1):80.	Reactogenicity of AS03-adjuvanted H5N1 vaccine was measured through AEs and quality-adjusted life-day (QALD) scores from quality of life questionnaires. No safety concern was identified. Pain and muscle ache were most commonly reported solicited AEs.
Oshansky CM et al. Safety and immunogenicity of influenza A(H5N1) vaccine stored up to twelve years in the National Pre-Pandemic Influenza Vaccine Stockpile (NPIVS). Vaccine. 2019 Jan 14;37(3):435-443.	Biomedical Advanced Research and Development Authority (BARDA) conducted a randomized, double-blinded Phase 2 study with the oldest stockpiled influenza A (H5N1) antigen, stored over the previous 10-12 years administered with or without MF59 adjuvant, stored over the previous 2-7 years at the time of vaccination. Stockpiled vaccines were well-tolerated, AEs were generally mild. Compared to unadjuvanted vaccine, greater peak antibody responses were observed in subjects who were vaccinated with MF59-adjuvanted vaccines, regardless of antigen dose. Vaccination with the A(H5N1) vaccine antigen also resulted in cross-reactive antibody responses to contemporary circulating strains of A(H5) influenza viruses. Vaccines were immunogenic when administered as 2-dose regimen in healthy adults, despite extended storage of HA antigen or MF59 adjuvant, and there was no drop in immunogenicity to the oldest stockpiled A(H5N1) vaccine.
Howard LM et al. Cell-Based Systems Biology Analysis of Human AS03-Adjuvanted H5N1 Avian Influenza Vaccine Responses: A Phase I Randomized Controlled Trial. PLoS One. 2017 Jan 18;12(1):e0167488.	Cell-based systems approach was used to investigate mechanisms of action for H5N1 pandemic influenza vaccines with and without AS03-adjuvant. Both vaccines were well-tolerated.
Guo Q et al. Immunogenicity and Safety of Pandemic Influenza H5N1 Vaccines in Healthy Adults through Meta-Analysis. Cell Physiol Biochem. 2016;40(5):921-932.	Pandemic H5N1 avian influenza vaccines surveyed in meta-analysis were well tolerated without serious adverse reactions.

8 CONCLUSION

This postmarketing pediatric safety review was triggered by the September 9, 2016 approval to extend the age range for use of Q-Pan H5N1 to include persons 6 months through 17 years of age. Q-Pan H5N1 is included in the U.S. Strategic National Stockpile and will be distributed by the US government in the event of an H5N1 pandemic. In the absence of an H5N1 influenza virus pandemic, no dose has been distributed to the population, and there are no adverse event reports submitted to VAERS. No new safety concerns are identified in the review of periodic safety reports or literature.

9 RECOMMENDATIONS

FDA recommends continued routine safety monitoring of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted (Q-Pan H5N1).