MEMORANDUM

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Subject: Fluarix Quadrivalent Pediatric Safety and Utilization Review for the Pediatric Advisory Committee (PAC) Meeting
         March 24, 2015

Sponsor: GlaxoSmithKline Biologicals

Product: Fluarix Quadrivalent (Influenza Virus Vaccine)

STN: 125127

Indication: For active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. Fluarix Quadrivalent is approved for use in persons 3 years of age and older.
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 a given year - two A virus strains most common in humans and a B strain. Two 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 influenza formulations are designed to protect against both B strains, providing additional coverage.

1.2 Regulatory History

Fluarix (Trivalent)
On August 31, 2005, the US Food and Drug Administration (FDA) granted accelerated approval for Fluarix, trivalent inactivated influenza virus vaccine, for active immunization for the prevention of disease caused by three influenza viruses (two subtypes A and one type B) contained in the vaccine for adults 18 years of age or older. Based on confirmatory studies, the FDA on October 2, 2009 granted full approval of Fluarix for the same indication. On October 19, 2009, the FDA approved expanded age usage for Fluarix to include individuals 3 years of age and older. FDA has not required any postmarketing study of Fluarix in the approved age range for any safety reason, but a pregnancy registry was established in 2011, is ongoing and has not identified any safety issues to date.

On September 22, 2011, the Fluarix Pediatric Safety and Utilization Review was presented to the Pediatric Advisory Committee (PAC), and the committee concurred with the Agency that continued routine safety monitoring was appropriate as no new safety concerns were identified in children in the initial 18-month approval period.

Fluarix Quadrivalent
Fluarix Quadrivalent is a seasonal influenza vaccine indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine in persons 3 years of age and older. Fluarix Quadrivalent was approved by the FDA on December 14, 2012. Fluarix Quadrivalent contains 60 micrograms (mcg) hemagglutinin (HA) per 0.5 mL dose, in the recommended ratio of 15 mcg HA of each of 4 influenza virus strains (two A subtypes and two B types). The two A subtypes and one of the B types are identical to those contained in Fluarix (trivalent formulation). A second B type is included in Fluarix Quadrivalent to provide added coverage. Influenza strains are identified according to USPHS requirements for the relevant influenza season.

Fluarix Quadrivalent is formulated without preservatives and does not contain thimerosal.

The US Advisory Committee on Immunization Practices (ACIP) recommendation of August 15, 2014, recommends routine influenza vaccination for all persons aged ≥ 6 months.

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 initial licensure 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 December 14, 2012 approval of Fluarix Quadrivalent and this review covers the period from the date of approval through June 30, 2014. However, because this product was not distributed in the US until the 2013-2014 influenza season, the actual period of use and corresponding safety data is from July 1, 2013 through June 30, 2014, the first influenza season in which Fluarix Quadrivalent was distributed in the US.

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 reported in the review period were attributed to Fluarix Quadrivalent. 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, and a review of the published literature.

3. MATERIALS REVIEWED

3.1 Vaccine Adverse Events Reporting System (VAERS)
- VAERS reports for Fluarix Quadrivalent submitted July 01, 2013 - June 30, 2014

3.2 Manufacturer’s Submissions
- Product distribution data
- Pharmacovigilance Plan submitted February 14, 2012 (STN 125127.513)
- Fluarix Quadrivalent Periodic Adverse Event Reports from licensure through July 11, 2014
- Fluarix Quadrivalent Prescribing Information last revised June 2014

3.3 FDA Documents
- Fluarix Quadrivalent Approval Letter, dated December 14, 2012

3.4 Publications
- Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the ACIP - U.S., 2014-15 Influenza Season
  http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6332a3.htm

4. LABEL CHANGES IN REVIEW PERIOD
There were no label changes related to safety concerns during the review period.

5. PRODUCT UTILIZATION DATA
GlaxoSmithKline reported that from July 1, 2013 – June 30, 2014, there were 7,806,183 doses of Fluarix Quadrivalent distributed in the US. Note that the number of doses distributed is an estimate of the number of patients vaccinated since all the distributed doses may not have been administered to patients. No data are available for pediatric-specific utilization.
6. PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

This section describes GlaxoSmithKline’s pharmacovigilance plan (PVP). From pre-licensure clinical studies, there were no important identified risks for Fluarix Quadrivalent. During the postmarket review period there have been no new identified risks. As Fluarix Quadrivalent is manufactured using the same process as that for Fluarix and contains the same influenza antigens as Fluarix, with the addition of a second B strain of the complementary B lineage, the sponsor considers the adverse events that are potential risks for Fluarix as potential risks for Fluarix Quadrivalent as well. Thus, febrile seizures, Bell’s palsy and Guillain-Barré Syndrome are considered potential risks for Fluarix Quadrivalent and will be evaluated and reported by the sponsor in ongoing periodic safety update reports.

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 (Armstrong 2011; Therapeutic Goods Administration 2010). 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 (Mutsch 2004), although a subsequent, well-designed epidemiological study did not show an association with other inactivated influenza vaccines and the development of Bell’s palsy (Stowe 2006). Guillain-Barré Syndrome (GBS) was associated with use of an A/New Jersey 1976 influenza vaccine in anticipation of a swine influenza epidemic (Schonberger 1979). 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 (Stowe 2009). 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.

There were no phase IV postmarketing studies planned for Fluarix Quadrivalent at or since the time of licensure.

A Pregnancy Registry has been established, but no data are yet available. The registry will prospectively enroll women who receive Fluarix Quadrivalent 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, gender, 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. A final study report will be submitted 18 months from the submission of the fifth annual PSUR on June 14, 2019. Enrollment will continue after submission of the final study report until CBER review and determination that the registry can be discontinued.
7. ADVERSE EVENT REVIEW

7.1 Methods
A search of the Vaccine Adverse Event Reporting System (VAERS) was performed for adverse event reports following Fluarix Quadrivalent between December 14, 2012 and June 30, 2014. VAERS is a spontaneous adverse event reporting system with inherent limitations including underreporting, delayed reporting, variable report quality and accuracy and difficulty assessing causality. All US serious adverse events occurring in children through 17 years of age were individually reviewed.

7.2 Results
The results of the VAERS search of adverse events after Fluarix Quadrivalent during the review period are listed in Table 1, below. Deaths, serious and non-serious reports are reviewed in detail in sections 6.2.1, 6.2.2 and 6.2.3 respectively.

<table>
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<th>Non-Serious</th>
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<tr>
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Table 1 summarizes the 308 adverse event reports submitted to VAERS after FLUARIX QUADRIVALENT, overall and by age. A total of 72 pediatric reports involving children 0 through 17 years of age, all domestic, included one death report and two non-fatal serious reports.

7.2.1 Deaths
No deaths were attributed to vaccination with Fluarix Quadrivalent.

Pediatric death
One pediatric death was reported in the review period: five months after receiving Fluarix Quadrivalent, a 10 year old male developed a fever, sore throat and cough. 6(6) days later he was found unresponsive at home with fixed and dilated pupils and attempted resuscitation efforts were ultimately unsuccessful. He experienced atrial fibrillation, atrial flutter and ventricular tachycardia, cardiac shock, cardiac arrest, multi-organ failure and vaccination failure. His medical history was significant for heterotaxy syndrome including congenital cardiac malformations and asplenia, multiple cardiac surgeries, right frontal and parietal lobe infarctions, placement of an implantable cardioverter / defibrillator / pacer. A request for autopsy was declined. No cause of death was reported but final diagnoses were listed as infection with Influenza Type B and ventricular tachycardia, in this asplenic,
immunocompromised individual with multiple co-morbid conditions.

Adult death
One adult death was reported in the review period. A 45 year old male was hospitalized with severe weakness 12 days after vaccination with Fluarix Quadrivalent, consistent with Guillain-Barré, and developed pulseless electrical activity resulting in death b(6) days after vaccination. His death certificate listed the cause of death as pulmonary embolism secondary to deep vein thrombosis, immobilization and hospitalization.

7.2.2. Non-fatal serious reports
Non-fatal Serious Adverse Events in Children 0-17 years of age
A 17 year old male driver was involved in a non-fatal motor vehicle accident when he crossed the road precipitating a head-on collision with another vehicle within less than an hour of receiving two vaccinations, including Fluarix Quadrivalent. He had no memory of the accident, but “awoke” in his car after the accident. After medical evaluation he was discharged to the care of his parents for overnight observation and intermittent wakening. No further information was submitted.

7.2.3 Non-serious Reports
Most non-serious reports were for labeled events and were consistent with the known profile of influenza vaccines. In the pediatric age group the most commonly reported adverse events were: Injection site erythema (N=14), Injection site swelling (N=10), Pyrexia (N=8), Erythema (N=7), Dizziness (N=5), Injection site warmth (N=5), Erythematous rash (N=5), Skin warm (N=5), Urticaria (N=5) and Vomiting (N=5).

7.3 Data Mining
Data mining was conducted using the US Vaccine Name run from Empirica Signal software version 7.2 to evaluate whether any events following use of Fluarix Quadrivalent were disproportionally reported, compared to other drugs in the VAERS database. Data mining covers the initial 18-month postmarketing period for this product, from initial licensure through the data lock point of 30 June 2014. The background database contains VAERS reports since 1990. Data mining findings are subject to a number of potential limitations and do not imply causality. No data mining alerts for disproportional reporting were identified for Fluarix Quadrivalent.

7.4 Periodic Adverse Event Review (PAER)
The PAER for Fluarix and Fluarix Quadrivalent covering the period May 1, 2013 to April 30, 2014, was reviewed. No additional safety issues were identified.

8. LITERATURE REVIEW

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 (Varricchio 2004). VAERS can assess early indicators of a possible vaccine safety problem that present as new or unusual adverse events or patterns of reports (Salmon 2011).

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 (Martin 2013). 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 (Burwen 2012).

Established in 1990, the Vaccine Safety Datalink (VSD) is a collaborative project between the Centers for Disease Control and Prevention (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 (McNeil 2014, Kawai 2014).

**Safety Signal Evaluation**
FDA, CDC, and CMS can use 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 they can determine the magnitude of the association.

In addition to seasonal surveillance for pre-specified adverse events of interest, VSD (Tse 2012) and CMS (Polakowski 2013) databases have been used to evaluate safety signals for flu 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 flu vaccines. 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).

10. CONCLUSION
This comprehensive postmarketing safety review of passive surveillance adverse event reports, Periodic Adverse Experience Reports and the published literature for Fluarix Quadrivalent 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 Fluarix Quadrivalent.

11. RECOMMENDATIONS
FDA recommends continued routine safety monitoring of Fluarix Quadrivalent. No further regulatory action is indicated at this time.

REFERENCES


Vaccine Adverse Reporting System: http://www.cdc.gov/vaccinesafety/Activities/vaers.html

Vaccine Safety Datalink: http://www.cdc.gov/vaccinesafety/Activities/vsd.html