MEMORANDUM

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Through: Craig Zinderman, MD, MPH
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From: Jane Woo, MD, MPH

Subject: FluMist Quadrivalent: Pediatric Safety and Utilization Review

Applicant: MedImmune, LLC

Product: FluMist Quadrivalent (Influenza Vaccine Live, Intranasal)

STN 125020

Indication: For active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine, for use in individuals 2 through 49 years of age

Meeting Date: Pediatric Advisory Committee Meeting, March 24, 2015
1. Introduction

On June 17, 2003, the US Food and Drug Administration licensed trivalent influenza vaccine live attenuated, intranasal (FluMist) for active immunization for the prevention of disease caused by influenza A and B viruses in healthy children and adolescents, 5 through 17 years of age, and healthy adults, 18 through 49 years of age. On September 19, 2007, the age indication was expanded to include children 2 through 4 years of age. On February 29, 2012, FluMist Quadrivalent was approved for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine, for use in individuals 2 through 49 years of age. The quadrivalent formulation includes two influenza A subtype viruses and two type B viruses. The approval of FluMist Quadrivalent is the trigger for this pediatric utilization and safety review for the Pediatric Advisory Committee (PAC).

Product description

FluMist Quadrivalent (influenza vaccine live, intranasal) is a live quadrivalent vaccine for administration by intranasal spray. Each pre-filled FluMist Quadrivalent sprayer contains a single 0.2 mL dose. For the 2013-2014 and 2014-2015 influenza seasons, each 0.2 mL dose contains live attenuated influenza virus reassortants of each of the four strains:

- A/California/7/2009 (H1N1)
- A/Texas/50/2012 (H3N2) (an A/Victoria/361/2011-like virus)
- B/Massachusetts/2/2012 (B/Yamagata/16/88 lineage)
- B/Brisbane/60/2008 (B/Victoria/2/87 lineage)

For the 2013-14 influenza season, the Advisory Committee on Immunization Practices (ACIP) issued the following recommendation:

Routine annual influenza vaccination is recommended for all persons aged ≥6 months. No preferential recommendation is made for one influenza vaccine product over another for persons for whom more than one product is otherwise appropriate. ⁱ

For the 2013-14 influenza season, the American Academy of Pediatrics (AAP) issued the following recommendation:

The American Academy of Pediatrics (AAP) recommends annual seasonal influenza immunization for all people, including all children and adolescents, 6 months of age and older during the 2013–2014 influenza season. Both trivalent and quadrivalent influenza vaccines are licensed and available in the United States for the 2013–2014 season. Neither vaccine formulation is preferred over the other. ²

2. Objective

The objective of this memorandum for the 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]. This review includes the period from approval of FluMist Quadrivalent, February 29, 2012, to June 30, 2014. Please note that distribution of FluMist Quadrivalent vaccine began in fall 2013, so the review period covers the first influenza season (2013-14) during which the product was distributed.
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 were identified. During this review period, there were no reports of pediatric deaths that were attributed to FluMist Quadrivalent. The product does not have a requirement for a post-marketing study or Risk Evaluation and Mitigation Strategy, and there have been no label changes regarding safety. 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 FluMist Quadrivalent (February 29, 2012 – June 30, 2014)

3.2 Manufacturer’s Submissions
• US package insert, July 2013 and July 2014
• Flumist quad distribution data for OPTPAC 2015, submitted September 29, 2014
• Sponsor’s Pharmacovigilance plan: risk-mgmt-plan, dated April 11, 2011
• Periodic Benefit-Risk Evaluation Reports (submission tracking numbers 125020.2112, 125020.2176, 125020.2196)

3.3 FDA Documents
• Approval letter issued on February 29, 2012 (BLA 125020/1668)
• OBE/DE memorandum: pharmacovigilance plan review 125020_1668_woo.pdf, February 2, 2012
  125020_1668_addendum_woo.pdf, February 21, 2012

3.4 Publications
PubMed search for “FluMist” conducted on October 1, 2014

3.5 Recommendations of the Advisory Committee on Immunization Practices
1 Recommendations of the American Academy of Pediatrics
Institute of Medicine: Adverse effects of vaccines: evidence and causality

4. Label changes in review period
There were no label changes for FluMist Quadrivalent related to safety concerns during the review period.

5. Product utilization data
MedImmune states that 12,892,109 doses of FluMist Quadrivalent were distributed in the US from February 29, 2012 to June 30, 2014. The number of doses distributed is an estimate of
the number of patients vaccinated, since doses may have been distributed without being administered to patients. The manufacturer does not have definitive data regarding vaccine utilization for specific age groups.

6. Pharmacovigilance by MedImmune

The sponsor’s Pharmacovigilance Plan for FluMist Quadrivalent states that there are two important identified risks: wheezing in children under the age of two years and hypersensitivity (including anaphylaxis). In clinical trials of FluMist trivalent versus inactivated influenza virus vaccine administered intramuscularly, the risks of hospitalization and wheezing were increased among children aged 6-23 months. Through 42 days post last vaccination, wheezing was higher after FluMist (5.9% versus 3.8%). Through 180 days post last vaccination, hospitalization due to any cause was higher after FluMist (4.2% versus 3.2%).

The package insert for Flumist Quadrivalent includes the following statements:

• In clinical trials, risks of hospitalization and wheezing were increased in children younger than 2 years of age who received FluMist (trivalent Influenza Vaccine Live, Intranasal).
• Children younger than 5 years of age with recurrent wheezing and persons of any age with asthma may be at increased risk of wheezing following the administration of FluMist Quadrivalent.

The Benefit-Risk Analysis Evaluation in the sponsor’s Periodic Benefit-Risk Evaluation Report, for the period December 17, 2013 to June 16, 2014, states that the following are considered important potential risks: Guillain-Barré syndrome, Bell’s palsy, seizures, encephalitis, neuritis, vasculitis, vaccine failure, and cataplexy/narcolepsy. Additional potential risks listed in the Pharmacovigilance Plan for FluMist Quadrivalent include secondary transmission to immunocompromised individuals and inadvertent vaccination of immunocompromised individuals, which are potential risks for live viral vaccines in general.

The clinical trials for FluMist Quadrivalent, which were conducted in 2,312 predominantly healthy children aged 2-17 years and 1,800 adults aged 18-49 years, did not raise any safety concerns. However, the sponsor states that FluMist Quadrivalent has not been thoroughly investigated in individuals with severe asthma, pregnant or lactating women, immunocompromised patients, children under 24 months of age, elderly individuals, and individuals with severe chronic diseases.

6.1 Periodic Benefit-Risk Evaluation Reports (PBRERs)

The manufacturer’s PBRERs do not suggest any change in the vaccine’s overall benefit-risk profile. Specifically, the sponsor has not identified any new safety signals, nor any risks or potential risks that were not already identified at the time of FluMist Quadrivalent approval. The sponsor has not identified any clusters of unusual serious adverse events or changes in frequency of reported adverse events. Moreover, no new safety issues have been identified in the sponsor’s ongoing studies of FluMist Quadrivalent (please see below).

6.2 Postmarketing Commitments

The approval letter dated February 29, 2012 includes the following safety-related Postmarketing Commitment:
You have agreed to conduct an observational postmarketing safety surveillance study of FluMist Quadrivalent in children 2 years through 8 years of age. The study is designed to evaluate rates of medically attended events in a minimum of 10,000 FluMist Quadrivalent recipients, compared to non-randomized comparison groups. The study will be completed by June 30, 2018 and the final study report will be submitted by June 30, 2019.

This study, which will utilize administrative claims data from Kaiser Permanente of Northern California, will assess safety-related events in children 2 through 8 years of age. This group includes the age range—children younger than 5—that the package insert states may be at increased risk of wheezing. The PBRER covering December 17, 2013 to June 16, 2014 stated that enrollment in Study MA-VA-MEDI3250-1115 ended on January 13, 2014, and the enrollment goal was met.

7. Vaccine Adverse Event Reporting System

7.1 The Vaccine Adverse Event Reporting System (VAERS)

The Vaccine Adverse Event Reporting System (VAERS) was searched for events following use of FluMist Quadrivalent reported from February 29, 2012 through June 30, 2014. Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, variable quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups.

The tables below summarize VAERS reports for FluMist Quadrivalent received during the review period.

Table 1. VAERS Reports for FluMist Quadrivalent (February 29, 2012 – June 30, 2014)

<table>
<thead>
<tr>
<th>Age</th>
<th>Serious</th>
<th>Deaths</th>
<th>Non-Serious</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>US</td>
<td>Foreign</td>
<td>US</td>
<td>Foreign</td>
</tr>
<tr>
<td>&lt; 2 years</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2-17 years</td>
<td>41</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>≥ 18 years</td>
<td>16</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>62</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

No deaths were attributed to vaccination with FluMist Quadrivalent. One death was reported during the review period. A 15-year-old white female developed a headache b(6) weeks after immunization with FluMist quadrivalent and human papillomavirus vaccine (types 6, 11, 16, and 18). She went to bed early and was unresponsive the following morning. Emergency services were contacted, and the patient was declared dead. The final autopsy report listed the cause of death as complications of cerebellar vascular tumor and intraparenchymal and subarachnoid hemorrhage. There was no evidence of bacterial or viral infection.
There were 42 serious adverse events in children under 18 years of age, including individuals who were younger than the indicated age range of 2-49 years of age.

Table 2. VAERS Reports for FluMist Quadrivalent (February 29, 2012 – June 30, 2014): Serious Adverse Events in Children Under 18 Years of Age

<table>
<thead>
<tr>
<th>Principal Adverse Event*</th>
<th>n = 42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system conditions</td>
<td></td>
</tr>
<tr>
<td>Meningitis, encephalitis, encephalopathy</td>
<td>7</td>
</tr>
<tr>
<td>Seizure</td>
<td>5</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>2</td>
</tr>
<tr>
<td>Other neurological condition</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory conditions</td>
<td></td>
</tr>
<tr>
<td>Wheezing, asthma, respiratory distress</td>
<td>4</td>
</tr>
<tr>
<td>Influenza</td>
<td>3</td>
</tr>
<tr>
<td>Immunologic disorders</td>
<td></td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>3</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>3</td>
</tr>
<tr>
<td>General signs, symptoms, conditions</td>
<td></td>
</tr>
<tr>
<td>Fever and vomiting</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>2</td>
</tr>
<tr>
<td>Hematologic condition</td>
<td>2</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>1</td>
</tr>
<tr>
<td>Events related to vaccine administration</td>
<td></td>
</tr>
<tr>
<td>Injection site reaction (concomitant vaccine)</td>
<td>5</td>
</tr>
</tbody>
</table>

*Based on clinical review of the VAERS report, follow-up reports, medical records, and other relevant documentation, each case was classified according to the patient’s primary adverse event. Based on review of the reported signs, symptoms, and diagnoses, the most important clinical entity was determined to be the principal adverse event.

During the review period, VAERS received seven serious reports of meningitis, encephalitis, or encephalopathy among individuals under the age of 18 years. The seven children ranged in age from 4 to 12 years, and the onset of neurological symptoms ranged from 5 hours to 9 weeks after vaccination with FluMist Quadrivalent. The number of reported cases of neurological conditions is small relative to the widespread use of Flumist Quadrivalent. Given the background risk in the indicated population, these conditions may be temporally associated with vaccination and do not necessarily indicate an association with vaccination status. The Postmarketing Experience section of the manufacturer’s package insert for FluMist Quadrivalent lists meningitis, eosinophilic meningitis, and vaccine-associated encephalitis. Based on a review of epidemiologic and mechanistic evidence, the Institute of Medicine’s Committee to Review Adverse Effects of Vaccines has concluded that the evidence is inadequate to accept or reject a causal relationship between influenza vaccine and encephalitis, encephalopathy, acute disseminated encephalomyelitis, seizures, and Guillain-Barré syndrome.3

In the review period, there were 4 serious reports of wheezing or asthma among individuals ranging in age from 14 months to 6 years. One of them was noted to have a history of asthma. As noted above, the package insert for Flumist Quadrivalent includes wheezing and a warning that children younger than 5 years old with a history of wheezing or asthma may be at
increased risk of wheezing. Given the background risk of asthma in the indicated population, the number of reported cases is small relative to the widespread use of Flumist Quadrivalent.

    General symptoms such as fever were observed in the prelicensure clinical trials of both the trivalent and quadrivalent formulations of FluMist, and are listed in the product label.

7.2 Data mining was conducted to evaluate whether any events following the use of FluMist Quadrivalent were disproportionally reported, compared to other vaccines in the VAERS database. The background database contains VAERS reports since 1990. 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. As of July 7, 2014, data mining in Empirica Signals Management for FluMist Quadrivalent (2013-14) using Empirica Signals Management software revealed an alert for disproportional reporting for the following adverse event terms:

    *Respiratory tract congestion, Rhinorrhea, Sneezing*

    Most reports of these events were non-serious. Symptoms resembling those of upper-respiratory infections were observed during the clinical trials for the trivalent vaccine and are listed in the package insert for both Flumist and FluMist Quadrivalent.

    *Accidental exposure to product, Drug administered to patient of inappropriate age, Drug administration error, Expired drug administered, Extra dose administered, Underdose*

    There were 210 reports that described vaccination errors, e.g., administration of FluMist Quadrivalent to individuals who were outside the age indication of 2-49 years, administration of product that was past its expiration date, etc. Most reports were not associated with an adverse event. All of the reports were non-serious, except the following: a 40-year-old healthcare worker with a history of asthma developed a life-threatening allergic reaction while administering FluMist Quadrivalent during a school-based vaccination clinic. She received epinephrine in the emergency department and reportedly recovered.

8. Literature review

    A PubMed search for “live attenuated influenza vaccine” on January 6, 2015 yielded 1289 publications. Many articles address vaccine recommendations and public health policy, and others concern experiments in mice or other non-humans. Adding the search term “safety” reduces the total to 81. After review of the titles or abstracts, the following 7 articles were published between February 29, 2012 and June 30, 2014, and are the most relevant to the safety of Flumist Quadrivalent.


The articles do not suggest any safety concerns about FluMist Quadrivalent.

9. Safety surveillance for influenza vaccines

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

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. 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. 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.⁸

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.⁹ This surveillance includes approximately 4-5 adverse events each flu season and involves live and inactivated vaccines.¹⁰,¹¹

**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, VSD¹² and CMS¹³ 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.¹⁴ The PRISM system uses the FDA’s Sentinel Distributed Database which includes a population exceeding 100 million.

10. Conclusion

This comprehensive postmarketing safety review of passive surveillance adverse event reports, Periodic Benefit-Risk Evaluation and the published literature for FluMist 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 received the vaccine. Most adverse event reports in pediatric patients were non-serious. No unusual frequency, clusters, or other trends were identified that would suggest a new safety concern in patients under the age of 18. The FluMist Quadrivalent package insert adequately reflects the known safety profile.

11. Recommendations

FDA recommends continued monitoring of FluMist Quadrivalent. No further regulatory action is indicated at this time.
6 http://www.cdc.gov/vaccinesafety/Activities/vaers.html ; accessed 12/22/14
9 http://www.cdc.gov/vaccinesafety/Activities/vsd.html ; accessed 12/22/14