SUMMARY BASIS FOR REGULATORY ACTION

Date: Feb 29, 2012

From: Zhiping Ye, MD., Ph.D, Chair of the Review Committee, DVP/OVRR

sBLA/STN: 125020/1668

Applicant Name: MedImmune LLC

Date of Submission: April 5, 2011

Refusal to File Letter Issued: April 29, 2011

Application Filed Over Protest: May 26, 2011

Proprietary Name: FluMist® Quadrivalent

Established Name: Influenza Vaccine Live, Intranasal

Indication: 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 persons 2 through 49 years of age

Recommended Action: Approval

Signatory Authorities Action: Approval

Offices Signatory Authority: Wellington Sun, M.D., Director, Division of Vaccines and Related Product Applications/Office of Vaccines Research and Review

√ **I concur with the summary review.**

□ **I concur with the summary review and include a separate review to add further analysis.**

□ **I do not concur with the summary review and include a separate review.**

Specific documentation used in developing the SBRA	Reviewer Name – Document Date
Clinical Review	Meghan Ferris, M.D. – 2/2012
Pharmacovigilance Review	Jane Woo, M.D. – 2/2012
Postmarketing effectiveness	Hector Izurieta, M.D. – 12/2011
Statistical Review	Sang Ahnn, Ph.D. – 1/2012
CMC Product Review	Christian Sauder, PhD. – 2/2012
CMC/Testing Review	Anil Choudhary, PhD. – 2/2012
CMC/Lot Release	Karen Campbell, - 2/2012
CMC/Facility	Chiang Syin, Ph.D. – 2/2012
Biomonitoring (BIMO) Review	Lillian Ortega – 12/2011
Toxicology Review	Steven Kunder PhD. – 2/2012
Advertising and Promotional Labeling	Maryann Gallagher – 9/2011 Lisa Stockbridge, PhD – 2/2012

I. INTRODUCTION

Influenza Vaccine Live, Intranasal, FluMist®, a frozen formulation was approved on June 17, 2003. FluMist® contains three live attenuated viruses, an A/H1N1 strain, an A/H3N2 strain and a single B strain. The refrigerated formulation of FluMist® was approved on 05 January 2007.

In this supplement, the applicant seeks licensure for marketing a quadrivalent formulation of cold-adapted live attenuated influenza virus vaccine. The proprietary name of this new formulation is FluMist® Quadrivalent. This vaccine differs from the licensed trivalent FluMist® vaccine in that a second Influenza virus B strain is added such that both influenza virus B strain lineages (B/Victoria/2/87 and B/Yamagata/16/88) are included. The addition of the second B strain did not require major changes to the currently approved manufacturing process for the trivalent FluMist® formulation. ----------(b)(4)----------.

The proposed indication for FluMist® Quadrivalent is for active immunization for the prevention of disease caused by influenza viruses included in the vaccine, in persons aged 2 through 49 years. FluMist® Quadrivalent safety and immunogenicity were supported by data from one pivotal pediatric study and one pivotal adult study. An additional study in adults, considered by the applicant to be supportive, was performed using a different device for vaccine administration, rather than the licensed Becton-Dickinson Accuspray presentation.

Efficacy of FluMist® Quadrivalent is inferred based on a demonstration of non-inferiority to two different formulations of trivalent FluMist®, each one containing one of the two B strain components of FluMist® Quadrivalent.

MedImmune LLC submitted this supplement to their biologics license application (sBLA) 125020.1668 on April 5, 2011 to include a quadrivalent formulation of Influenza Vaccine Live, Intranasal. This sBLA included information on modification and validation of the ----------(b)(4)----------. The application also included clinical data on safety and immunogenicity of the product. Immunogenicity and safety data in the BLA are from three clinical studies conducted under IND -(b)(4)- (first submitted on December 2, 2008).

After initial review of the sBLA, on April 29, 2011, a Refusal to File letter was sent to the applicant notifying them that that the application was deficient for the purpose of filing. The applicant subsequently provided the deficient information and on May 26, 2011, requested in writing that the submission be Filed Over Protest. The application was filed on that date. The review clock was stopped on April 29, 2011, and was restarted on May 26, pushing back the original Action Due date 26 days from February 3, 2012, to February 29, 2012, corresponding to the number of days between the Refusal to File letter and receipt of a written request for File Over Protest.

During the review process, the committee extensively reviewed all sections of the application. In response to the committee's evaluation, MedImmune submitted over 30 amendments to the BLA supplement. The applicant provided satisfactory written responses to all the comments and questions from the reviewers. In support of our

approval recommendation, the review of the FluMist® Quadrivalent is summarized in the following sections.

II. VACCINE INFORMATION

The proposed indication and usage for FluMist® Quadrivalent is active immunization against disease caused by influenza A and B viruses in persons aged 2-49 years. Children 2 through 8 years of age should receive one or two doses depending on vaccination history. If two doses are given the interval between doses is approximately one month. Persons 9 through 49 years of age should receive a single dose.

The final FluMist® Quadrivalent product is a blend of four monovalent bulk strains of cold-adapted (*ca*), temperature sensitive (*ts*) and live, attenuated (*att*) and purified influenza viruses, which were diluted with cGAG (concentrated Gelatin-Arginine-Glutamate) Buffer and 1X SP (Sucrose Phosphate) Buffer. Table 1 lists these components per unit dose. ----------
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----------. The finished product is presented as a 0.2 mL unit dose (approximately 0.1 mL per nostril). Gentamicin sulfate ----------
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----------, resulting in a diluted residual concentration in the final product (<0.015 µg/mL). Each dose may also contain residual amounts of ovalbumin (< 0.24 mcg/dose), and ethylenediaminetetraacetic acid (EDTA) (< 0.37 mcg/dose). No substances of human origin are used in the manufacture of this formulation.

Table 1. List of Ingredients

NAME	QUANTITY*
Active ingredients	
1. Influenza A (H1N1) strain	7.0 $\pm$ 0.5 $\log_{10}$ FFU**
2. Influenza A (H3N2) strain	7.0 $\pm$ 0.5 $\log_{10}$ FFU
3. Influenza B strain (Yamagata Lineage)	7.0 $\pm$ 0.5 $\log_{10}$ FFU
4. Influenza B strain (Victoria Lineage):	7.0 $\pm$ 0.5 $\log_{10}$ FFU
Excipients	
Sucrose	13.68 mg
Dibasic Potassium Phosphate	2.26 mg
Monobasic Potassium Phosphate	0.96 mg
Gelatin Hydrolysate	2.00 mg
Arginine -------(b)(4)-------	2.42 mg
Monosodium glutamate	0.19 mg

* per 0.2 ml dose
** FFU – Fluorescent Focus Units as measured by Fluorescent Focus Assay.

III. CHEMISTRY, MANUFACTURING, AND CONTROL

Manufacturing processes, methods, specifications, and results of in-process and product tests were thoroughly reviewed.

Drug substance

The drug substance manufacturing process for FluMist® Quadrivalent is essentially the same as the licensed manufacturing process for FluMist® and therefore, drug substance sections are not included in this supplement.

Drug product

The drug product manufacturing process for FluMist® Quadrivalent is the same as that used for FluMist® with the exception of the inclusion of the additional B strain. No additional process steps are required and all critical process parameters, buffers, and excipients are the same for the FluMist® and FluMist® Quadrivalent manufacturing processes. Therefore, no additional process development studies were required for FluMist® Quadrivalent.

The in-process and release testing for FluMist® Quadrivalent are the same as those for FluMist®. The components, product contact materials and equipment used in the FluMist® Quadrivalent manufacturing process are the same as those used for FluMist®.

The analytical methods for the release of FluMist® Quadrivalent lots are the same as the methods for the release of FluMist® lots ----------
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The process validation studies were reviewed and they confirmed that the critical process parameters in the process were met. Additionally, all test results generated for the process validation/consistency lots were within specification. The data from the beginning, middle and end samples from each individual lot demonstrated the uniformity of the (b)(4)/Blend/Fill processes. These data demonstrate that the drug product manufacturing processes consistently yield a uniform product that is within the established quality criteria.

Description of Manufacturing Process of drug product

The finished drug product is a blend of four strains of monovalent bulk drug substance, stabilized with cGAG (concentrated Gelatin-Arginine-Glutamate) Buffer and diluted to final volume with 1X SP (Sucrose Phosphate) Buffer. Each of the four influenza viruses (A/H1N1, A/H3N2 and the two B strains) is formulated to yield a potency of 7.0 ± 0.5 log_{10} FFU per 0.2 mL dose. The final, blended product is aseptically filled as a 0.2 mL deliverable dose into ----------(b)(4)---------- AccuSpray nasal sprayer
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k. Specification(s)

Lot release tests are performed on samples collected at the bulk quadrivalent blend stage and filled quadrivalent blend in order to comply with the drug product specification. Sterility is performed on the bulk quadrivalent blend. Lot specific tests are performed on filled quadrivalent blend. The tests performed include -(b)(4)-, Identity, Ovalbumin, Potency, (b)(4), Color and Appearance, Endotoxin, General Safety/Abnormal Toxicity, and Sterility.

Lot Release Specification for Bulk Blend

Test	**Acceptance Criteria**
Sterility	No confirmed evidence of bacterial or mycotic contamination

Lot Release Specification for Filled Quadrivalent Blend

Test	**Acceptance Criteria**
(b)(4)	----(b)(4)----
Potency	H1N1: 7.0 ± 0.5 $\log_{10}$ FFU/Dose (0.2 mL) H3N2: 7.0 ± 0.5 $\log_{10}$ FFU/Dose (0.2 mL) B (Yamagata Lineage): 7.0 ± 0.5 $\log_{10}$ FFU/Dose (0.2 mL) B (Victoria Lineage): 7.0 ± 0.5 $\log_{10}$ FFU/Dose (0.2 mL)
Total potency	≤ 8.0 $\log_{10}$ FFU/Dose (0.2 mL)
Identity	Expected virus subtypes correctly identified
Endotoxin	Less than or equal to --(b)(4)--
Ovalbumin	Less than or equal to 1.2 µg/mL
-----(b)(4)-----	------(b)(4)------
Color and Appearance	----------(b)(4)----------
Sterility	No confirmed evidence of bacterial or mycotic contamination
General Safety/ Abnormal Toxicity	No evidence of toxicity or abnormality

Stability

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----------, each arm is then transferred to 2°C to 8°C storage to monitor the stability profile.

Consistency Lots

A clinical lot-to-lot consistency study was not required for this supplement, since FluMist® Quadrivalent is manufactured using the same process as FluMist®. The process validation lots at the intended commercial scale were manufactured and documented in the BLA supplement.

Lot Release and Marketing Plan

There is no hold step between the production of the final bulk vaccine and filling of final containers. Lot release protocols for final containers were submitted in support of the license application. All critical product tests will be reflected in the lot release protocol for the final container vaccine.

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Facilities review/inspection

No facility inspections were held to support the review and licensure of this product because the facilities have been routinely inspected for the manufacture of trivalent FluMist®.

Environmental Assessment

The applicant claimed a categorical exclusion to the environmental analysis requirements in accordance with 21 CFR Part 25.31(c). MedImmune indicated that there are no extraordinary circumstances, as described in 21 CFR Part 25.31, associated with this action. No potential adverse environmental impact is expected from the manufacture and use FluMist® Quadrivalent.

Post Marketing CMC Commitments

The applicant has agreed to the following CMC postmarketing commitments:

1. ----------(b)(4)----------.
2. ----------(b)(4)----------.

IV. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

The applicant conducted an intranasal toxicology study in ferrets to support the supplemental BLA for FluMist® Quadrivalent. The toxicology study used 3 doses, which were the same as the intended clinical dose. No treatment related effects were observed in this study.

An intranasal reproductive and developmental toxicology study in rats used the same dose with either 3 pre-mating or 3 pre- and 3 post-mating doses. No treatment-related findings were observed affecting fertility or mating performance, maternal health, gestation or post-natal development. No soft tissue or skeletal anomalies or variations were noted due to treatment. Pup survival, weight, sex were unaffected from birth through weaning. F1 generation physical and behavioral development appeared unaffected. These data support Category B in the Pregnancy section of the package insert.

Based on nonclinical toxicity and reproductive/developmental assessments of this submission, there are no significant nonclinical safety issues which prevent the approval of this BLA supplement.

V. CLINICAL PHARMACOLOGY

Mode of Action

Immune mechanisms conferring protection against influenza following receipt of FluMist® Quadrivalent vaccine are not fully understood; serum antibodies, mucosal antibodies, and influenza-specific T cells may play a role.

FluMist® Quadrivalent contains live attenuated influenza viruses that must infect and replicate in cells lining the nasopharynx of the recipient to induce immunity. Vaccine viruses capable of infection and replication can be cultured from nasal secretions obtained from vaccine recipients (shedding)

VI. CLINICAL/ STATISTICAL

Immunogenicity and Safety

FluMist® Quadrivalent is a vaccine indicated for active immunization for the prevention of disease caused by influenza A subtypes viruses and type B viruses. FluMist® Quadrivalent is approved for use in individuals 2 through 49 years of age. FluMist® Quadrivalent is administered as a single dose to individuals ≥ 9 years old and children 2 through 8 years old who have been previously immunized with influenza vaccine and as a 2 dose series in children 2 through 8 years old who have not been previously immunized with influenza vaccine. FluMist® Quadrivalent safety and immunogenicity were supported by data from one pivotal pediatric (2-17 years of age) study (MI-CP208) and one pivotal adult (18-49 years of age) study (MI-CP185). The two pivotal studies raised no new safety concerns. In general, the safety and reactogenicity profile of FluMist® Quadrivalent appeared similar to that of FluMist® in both adults and children. Runny/stuffy nose was the most frequently reported solicited reaction, and the median duration of any reactogenicity symptoms was $\underline{\leq}$ 4 days. An additional study in adults, considered by the applicant to be supportive, was performed using a different device for vaccine administration, rather than the licensed Becton-Dickinson Accuspray presentation. This device is not approved for vaccine administration of FluMist® Quadrivalent. The studies were conducted in the United States.

Efficacy of FluMist® Quadrivalent is inferred from data demonstrating the clinical efficacy of trivalent FluMist in children and the effectiveness of FluMist in adults. This supplement includes data from a non-inferiority comparison of immune response with two different formulations of trivalent FluMist®, each one containing one of the two B strain components of FluMist® Quadrivalent. The primary endpoint was an upper

bound of the 95% confidence interval (CI) of the ratio of FluMist® GMTs divided by FluMist® Quadrivalent of $\leq$ 1.5 for all 4 strains included in the FluMist® Quadrivalent. All pre-specified primary endpoints were met. The immune response to FluMist® Quadrivalent met the prespecified criteria for non-inferiority compared to that elicited by trivalent FluMist®. These data also showed that the addition of a second B strain did not result in immune interference to the other strains included in the vaccine.

The applicant has provided a Pharmacovigilance Plan and committed to conduct a post marketing study to evaluate safety in children 2-8 years of age and a post marketing study to further evaluate effectiveness in children 2-17 years of age.

Study MI-CP208

In the pivotal pediatric study, a total of 2,312 subjects were randomized (by age strata; 2 to 8 years of age and 9 to 17 years of age) at a 3:1:1 ratio to receive either FluMist® Quadrivalent or 1 of 2 formulations of FluMist®, each containing a B strain that matched 1 of the 2 B strains in the FluMist® Quadrivalent vaccine. Among 2,312 subjects randomized, 2,305 received at least one dose of vaccine.

The results showed that after vaccination, the immune response to each of the 4 influenza vaccine strains contained in FluMist® Quadrivalent met the prespecified criteria for noninferiority compared to that elicited by trivalent FluMist®. No deaths and no SAEs considered to be related to investigational product were reported in study subjects. No SAEs occurred within 28 days of Dose 1. Within 28 days of Dose 2, 3 subjects reported 4 SAEs, but none of them were considered to be related to the investigational vaccines.

Subgroup analyses of immunogenicity by gender, race (white vs. non-white) or age (2-8 years vs. 9-17 years) did not show any remarkable difference in immunogenicity. Subgroup analyses of serious adverse events (SAE's) by gender, race (white vs. non-white), or age (2-8 years vs. 9-17 years) did not show any noteworthy difference in the distribution of SAE's.

Study MI-CP185

In the pivotal adult study, a total of 1,800 subjects (18-49 years of age) were randomized by site at a 4:1:1 ratio to receive a single dose of either FluMist® Quadrivalent or 1 of 2 formulations of FluMist®, each containing a B strain that matched 1 of the 2 B strains in the FluMist® Quadrivalent vaccine. Among 1,800 subjects randomized, 1,798 received a dose of vaccine. Immunogenicity analyses were performed on 1,770 subjects. The safety population included 1,796 subjects, and the evaluable safety population for solicited symptoms included 1,794 subjects.

The results showed that after vaccination, the immune response to each of the 4 influenza vaccine strains contained in FluMist® Quadrivalent met the prespecified criteria for noninferiority compared to that elicited by trivalent FluMist®. There were no SAEs considered to be related to the investigational product that occurred in subjects in the FluMist® Quadrivalent arm. There was an SAE of hypersensitivity (allergic reaction with brochospasm) considered to be related to the FluMist®/B/Victoria vaccine.

Subgroup analyses of immunogenicity by gender, race (white vs. non-white) or age (18-34 years vs. 35-49 years) did not show any remarkable difference in immunogenicity. Subgroup analyses of serious adverse events (SAE's) by gender, race (white vs. non-

white), or age (18-34 years vs. 35-49 years) did not show any noteworthy difference in the distribution of SAE's.

Risk Assessment

The two pivotal studies raised no new safety concerns. In general, the safety and reactogenicity profile of Q/LAIV appeared similar to that of FluMist® in both adults and children. Runny/stuffy nose was the most frequently reported solicited reaction, and the median duration of any reactogenicity symptoms was $\leq$ 4 days. Based on the information that is available at this time, a Risk Evaluation and Mitigation Strategy will not be required.

Post Marketing Commitments and Post Marketing Requirements

The postmarketing plans, subject to reporting requirements of 21 CFR 601.70, as specified by the epidemiological safety reviewer from the Office of Biostatistics and Epidemiology, and agreed to by MedImmune LLC, are as follows:

1. 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 of interest in a minimum of 10,000 FluMist® Quadrivalent recipients, compared to three non-randomized comparison groups.

   Final protocol submission date: April 30, 2013

   Study/trial completion date: June 30, 2018

   Final Report Submission date: June 30, 2019

2. To conduct an observational postmarketing case-control study of the effectiveness of FluMist® Quadrivalent in children 2 years through 17 years of age. The study is designed to compare the effectiveness of vaccination with FluMist® Quadrivalent to no vaccination and to vaccination with an inactivated influenza vaccine over four influenza seasons.

   Final protocol submission date: April 30, 2013

   Study/trial completion date: December 31, 2017.

   Final Report Submission date: December 31, 2018

PREA

The applicant requested that the requirement to study FluMist® Quadrivalent in all pediatric populations be waived for children younger than 2 years of age. This request was presented to the PeRC on December 14, 2011. Previous studies with the trivalent FluMist® demonstrated an increased risk of wheezing and hospitalization for pneumonia in children younger than 2 years of age in previous studies. Based on these data a partial waiver of pediatric studies in children younger than 2 years of age is justified for FluMist Quadrivalent. Safety and immunogenicity data support use of FluMist Quadrivalent in children 2 through 17 years of age.

Bioresearch Monitoring

Four clinical sites for study MI-CP 185 and MI-CP 208 were inspected. The inspections did not reveal problems that would impact the data submitted in the application.

VII. SAFETY

In two pivotal studies FluMist® Quadrivalent was administered to children 2-17 years of age and adults 18-49 years of age. Solicited adverse events were monitored during Days 0-14 post-vaccination; serious and non-serious unsolicited adverse events were monitored during Days 0-28 post-vaccination; and specific adverse events of interest (SAEs, new onset chronic disease) were followed for 6 months following the last immunization in these studies. The pivotal studies raised no new safety concerns. In general, the safety and reactogenicity profile of FluMist® Quadrivalent appeared similar to that of FluMist® in both adults and children. Runny/stuffy nose was the most frequently reported solicited reaction, and the median duration of any reactogenicity symptoms was $\leq$ 4 days.

VII. LABELING

Labeling and packaging were reviewed and a series of revisions were submitted to the BLA supplement. The current versions are acceptable for the approval of this supplement.

VIII. ADVISORY COMMITTEE MEETING

It was determined that review of the sBLA for FluMist® Quadrivalent by the Vaccines and Related Biological Products Advisory Committee (VRBPAC) was not required because of CBER's experience with the currently licensed FluMist® and because FluMist® Quadrivalent manufacturing is similar to the procedures used for the currently licensed FluMist® formulation. Furthermore, because our review of information submitted in the supplement, including the clinical study design and trial results, did not raise concerns or controversial issues which would have benefited from an advisory committee discussion, it was agreed that discussion of the review of this sBLA by the VRBPAC was not necessary.

XI. OTHER RELEVANT REGULATORY ISSUES

This BLA supplement is to approve the first Quadrivalent influenza vaccine to be marketed in the US. The influenza vaccine strains included in the FluMist® formulation have been recommended by the WHO and the Vaccines and Related Biological Products Advisory Committee.

X. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

1. *Recommended Regulatory Action*

Following the review of all supportive product and clinical data, it is the recommendation of the review committee to approve this application

2. *Risk/Benefit Assessment*

The quality, efficacy, and safety of this vaccine have been thoroughly reviewed and have been determined to be acceptable for use of this vaccine as indicated in the label. The benefits of using this vaccine are related to the efficacy for the prevention of Influenza infection in persons aged 2 through 49 as demonstrated in the results of the clinical studies.

3. *Recommendation for Postmarketing Risk Management Activities*

There was no recommendation for postmarketing risk management activities. See below for the postmarketing activities associated with the licensure of this formulation.

4. *Recommendation for Postmarketing Activities*

Postmarketing activities include studies that will be performed post-licensure. These studies are classified as either postmarketing requirements under Section 505(o) of the Food Drug and Cosmetic Act (FDCA), postmarketing commitments subject to 21 CFR 601.70 or postmarketing commitments not subject to 21 CFR 601.70. During the review of the BLA it was determined that no postmarketing requirement studies were necessary.

Two postmarketing clinical studies were discussed with MedImmune LLC. The first is an observational postmarketing safety surveillance study of FluMist® Quadrivalent in children 2 years through 8 years of age to evaluate rates of medically attended events of interest in a minimum of 10,000 FluMist® Quadrivalent recipients, compared to two other non-randomized comparison groups. The second is an observational postmarketing case-control study of the effectiveness of FluMist® Quadrivalent in children 2 years through 17 years of age compared to no vaccination and to vaccination with an inactivated influenza vaccine over four influenza seasons.

Two postmarketing CMC commitments were also discussed with MedImmune LLC.

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No other PMC's were requested.