Summary Basis for Regulatory Action

Date: May 26, 2011

From: R. Douglas Pratt, M.D. M.P.H., Review Committee Chair

BLA/ STN#: 125020.1465

Applicant Name: MedImmune LLC

Date Submission Received: July 28, 2010

Proprietary Name/ Established Name: FluMist

Proper Name: Influenza Virus Vaccine, Trivalent, Type A & B, Live, Cold-Adapted (CAIV-T)

Purpose of License Supplement: To revise the package insert to include new information about vaccine virus replication and shedding.

Recommended Action: Approval

Office Signatory Authority: Wellington Sun, M.D., Director, DVRPA

☐ **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.**

Review Committee

J.P. McWatters, Ph.D.	Regulatory Project Manager
Meghan Ferris, M.D., M.P.H.	Clinical Reviewer
Sang Ahnn, Ph.D.	Biostatistical Reviewer

1. Introduction

FluMist™ is a live, trivalent, intranasally administered vaccine indicated for prevention of influenza disease caused by the influenza viruses contained in the vaccine. FluMist is approved for use in healthy individuals age 2-49 years. It is distributed as 0.2 mL in a single use BD Accuspray ™ nasal sprayer containing 1 x $10^{6.5-7.5}$ FFU (fluorescent focus units) of each of the three influenza virus strains recommended on a yearly basis by the U.S.public health authorities. The FluMist vaccine strains are cold-adapted (*ca*), temperature-sensitive (*ts*), and attenuated (*att*); these properties are intended to allow the vaccine viruses to replicate in the nasopharynx and to restrict transmission of vaccine viruses.

The FluMist influenza vaccine strains replicate in the nasopharynx and can be recovered and cultured from respiratory secretions of vaccinated individuals (shed). The pattern and duration of shedding is important to understand because with prolonged shedding at high titer there is a theoretical risk of loss of attenuated phenotype, reassortment with wild-type influenza virus during influenza season, and transmission of vaccine virus to unvaccinated people, some of whom may be immunocompromised and/or at risk for complications of live viral infections.

MedImmune submitted this clinical supplement to their Biologics License Application (sBLA) to include new information in the package insert about replication and shedding of vaccine viruses among children and adults 6 months of age through 49 years of age, which encompasses the age range (2 years -49 years) for which FluMist is currently approved. The shedding studies in children and adults 5 through 49 years of age were conducted to fulfill a Post Marketing Commitment (PMC) to further characterize shedding in specified age groups, agreed upon at the time of approval of the original license application in 2003. These data were submitted to the BLA on January 16, 2007. The PMC was closed out in 2008, but the data were submitted in this sBLA to support their inclusion in the label.

2. Regulatory Background

FluMist was approved for use in healthy subjects 5-49 years of age in June 2003. Effectiveness of FluMist in children was demonstrated in randomized, controlled studies by prevention of culture-confirmed influenza disease. Effectiveness in adults was demonstrated by reduction in influenza-like disease that was not confirmed by identification of influenza virus. The safety evaluation in children found that FluMist recipients one and one-half to five years of age had increased rates of asthma/reactive airway disease in the 42 days after vaccination in the main safety study. The label included a warning that the vaccine was not to be administered to subjects with a history of asthma.

A formulation change was approved in January, 2006. The original frozen formulation required frozen storage until use. The new formulation (called liquid) does not require frozen storage. In making the change of formulation from frozen to liquid, the dosage volume was reduced from 0.5 mL to 0.2 mL and minor modifications were made in the excipients. Studies submitted in the current label supplement BLA used either frozen or liquid FluMist.

Extension of the indication to individuals 2 – < 60 months was approved on September 17, 2007. Vaccine effectiveness in this age group was based on efficacy in preventing culture-confirmed

clinical influenza in a comparative study to a U.S.-licensed inactivated influenza vaccine. The clinical review contributing to this approval also concluded that the use of FluMist should be limited to children 24 months of age and older because of differences in rates of hospitalizations, wheezing, and of other lower respiratory tract adverse events among children < 2 years of age.

3. Chemistry Manufacturing and Controls (CMC)

No changes to manufacturing processes or laboratory assay methods were made that are relevant to this supplement.

4. Non-clinical Pharmacology/Toxicology

Not applicable.

5. Clinical Pharmacology

No clinical pharmacology data were provided in the supplement.

6. Clinical/Statistical

Safety and shedding data from four clinical studies were included in the BLA supplement. Additionally, a publication with associated electronic datasets was submitted in support of a label claim regarding shedding in HIV positive subjects. The five shedding trials were conducted in various age groups. The 2 studies in healthy subjects were a Phase 2 study in 200 children 6 months to < 60 months of age (NCT 00344305), and a Phase 4 study in 345 subjects 5 – 49 years old (NCT00998491). In both of these studies, all subjects received FluMist. The other 3 shedding trials were conducted in subjects with some form of immunocompromise. In total, 156 immunocompromised subjects received FluMist in these trials: 24 subjects 1 – 7 years old with HIV infection, 122 subjects 5-17 years old with HIV infection, and 10 subjects 5 – 17 years old with cancer.

In the two studies of healthy subjects, nasal secretions were obtained daily for the first 7 days and every other day either through day 25 and on day 28, or through day 28. In the study of children 6 months to < 60 months of age, children shedding at day 25 or day 28 were to have additional shedding samples collected every 7 days until culture negative on 2 consecutive samples. Results of these studies, considered by the review team to be appropriate for inclusion in the package insert, are presented in the table below:

Characterization of Shedding in Specified Age Groups by Frequency, Amount, and Duration

Age	Number of Subjects	% Shedding[b]	Peak Titer ($TCID_{50}$/mL)[c]	% Shedding After Day 11	Day of Last Positive Culture
6 – 23 months[a]	99	89	< 5 log_{10}	7.0	Day 23[d]
24 - 59 months	100	69	< 5 log_{10}	1.0	Day 25[e]
5 - 8 years	102	50	< 5 log_{10}	2.9	Day 23[f]
9 – 17 years	126	29	< 4 log_{10}	1.6	Day 28[f]
18 - 49 years	115	20	< 3 log_{10}	0.9	Day 17[f]

[a] FluMist is not approved for use in children < 24 months of age [see *Adverse Reactions (6)*].
[b] Proportion of subjects with detectable virus at any time point during the 28 days.
[c] Peak titer at any time point during the 28 days among samples positive for a single vaccine virus.
[d] A single subject who shed previously on Days 1-3; $TCID_{50}$/mL was less than 1.5 log_{10} on Day 23.
[e] A single subject who did not shed previously; $TCID_{50}$/mL was less than 1.5 log_{10}.
[f] A single subject who did not shed previously; $TCID_{50}$/mL was less than 1.0 log_{10}.

In each age group, among subjects who shed, shedding was most often observed on days 2-3 post vaccination. Among the population for whom FluMist is currently approved for use, i.e., individuals 2-49 years of age (n = 443), vaccine virus titers did not exceed 1.5 log10 TCID50/mL after day 11, though some individuals shed vaccine strain virus as late as day 28 post-vaccination.

Although FluMist is not licensed for use in children younger than 24 months of age, shedding data for children 6 - < 24 months of age were included in the review and in the package insert because these data contribute to a better understanding of the kinetics of shedding of FluMist strains, and illustrate the higher proportion of children shedding in the youngest age group, and the decreasing proportion shedding with increasing age.

Safety and shedding data in immunocompromised children from three studies conducted were also submitted with this supplement. Two of these studies involved FluMist administration to a combined total of 146 HIV-infected children, 122 of whom were 5 - 17 years old (NCT00091702) and 24 of whom were ages 1 - 7 years. The remaining study (NCT00112112) involved FluMist vaccination of 10 mild to moderately immunocompromised children 5 - 17 years old who were receiving chemotherapy and/or radiation therapy, or who had received chemotherapy in the 12 weeks prior to enrollment. In each study, the frequency and duration of vaccine virus shedding among these immunocompromised children did not differ markedly from that seen in healthy children.

7. Safety

The clinical review of safety data from the studies submitted to this sBLA did not identify any new safety concerns that warrant revisions in labeling.

8. Advisory Committee Meeting

The Vaccines and Related Biologics Advisory Committee (VRBPAC) was not convened to discuss this supplement. Advice from VRBPAC was not thought to be critical to the review

because the data and proposed changes to labeling do not affect the indication or use of the vaccine or reveal major safety concerns.

9. Other Relevant Regulatory Issues

The data from studies included in this supplement satisfactorily fulfill STN 125020.0 post-marketing commitment # 3, which was to conduct a clinical study to investigate shedding of FluMist vaccine virus.

Pediatric Research Equity Act (PREA) and the Pediatric Review Committee (PeRC)
A pediatric assessment as defined by PREA and PeRC review was not required because the supplement did pertain to a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.

10. Bioresearch monitoring (BiMo) inspections

Data audits from the clinical sites of the shedding studies were not conducted.

11. Labeling

Changes to the package insert supported by this submission include:

- **14.4 Studies in Immunocompromised Individuals:** this subsection of the package insert has been modified to include shedding and safety data from studies in HIV infected children.
- **14.5 Shedding Studies:** this is a new subsection in the package insert which includes a table of new data about vaccine virus replication and shedding in healthy individual presented above.

In addition, minor corrections and editorial changes to labeling were considered appropriate.

12. Recommendations

The review committee recommends approval of this license application supplement to include revisions to the package insert.