PART 1 (COUNCIL DECISION 2002/813/EC)

SUMMARY NOTIFICATION INFORMATION FORMAT (SNIF) FOR RELEASES OF GENETICALLY MODIFIED ORGANISMS OTHER THAN HIGHER PLANTS IN ACCORDANCE WITH ARTICLE 11 OF Directive 2001/18/EC

A. GENERAL INFORMATION

1. Details of notification

a) Member State of notification Finland
b) Notification number B/FI/09/1MA
c) Date of acknowledgement of notification 2.10.2009
d) Name of the product (commercial and other names): Quadrivalent Live Attenuated Influenza Vaccine (Q/LAIV), Intranasal Trivalent Live Attenuated Influenza Vaccine (FluMist), Intransal
e) Title of the project MI-CP208, “A Randomized, Double-Blind Active Controlled Study to Evaluate the Immunogenicity of Quadrivalent Live Attenuated Influenza Vaccine in Children”.
f) Proposed period of release It is anticipated that enrollment will begin in the EU in April 2010 and will be completed by November 2010.

2. Notifier

Name of institution or company MedImmune, LLC

3. GMO characterization

a) Indicate whether the GMO is a:

Viroid	☐
RNA virus	☑
DNA virus	☐
bacterium	☐
fungus	☐
animal	☐
- mammals	☐
- insect	☐
- fish	☐
- other animal	☐ please specify phylum, class

other, please specify (kingdom, phylum and class)

b) Indicate the name and nature of each type of GMO contained in the product

Q/LAIV, live attenuated influenza vaccine, is a quadrivalent preparation for intranasal administration that contains 2 type A (i.e. A/H1N1 and A/H3N2) and 2 type B attenuated (*att*), cold-adapted (*ca*) and temperature sensitive (*ts*) reassortant strains of influenza virus. All the mutations responsible for these phenotypes were introduced through classical selective pressure and were made by natural processes. This organism is classified as genetically modified solely based on the modern manufacturing technique (ie reverse genetics) used to generate the vaccine seed. These strains are 6:2 genetic reassortants expressing the 6 internal genes from the master donor viruses (MDVs) and 2 gene segments encoding haemagglutinin (HA) and neuraminidase (NA) from contemporary wild type (*wt*) viruses. The vaccine strains for Q/LAIV to be used in Study MI-CP208 include A/H1N1, A/H3N2, B strain of Yamagata lineage and B strain of Victoria lineage. A/H1N1, A/H3N2, B strain of Yamagata lineage were produced using plasmid rescue techniques and are considered to be GMOs. The B strain of Victoria lineage was made using classical reassortment and thus is not a GMO. The strains produced by plasmid rescue are essentially identical to non-GMO strains made by conventional, non-recombinant, classical reassortment methods. Q/LAIV will be administered using Becton Dickinson Accuspray™ delivery device.

c) Genetic stability – according to Annex IIIa, II, A(10)

The genetic stability of the attenuated virus strains used in Q/LAIV have been previously demonstrated by evaluating the sequence data collected on 36 different monovalent bulk (MB) lots produced from 10 different MVSs used in the manufacture of US licensed FluMist. These data have shown that the nucleotide sequence of virus strains used in the vaccine did not vary following either one or two passage in eggs during manufacturing. Every vaccine intermediate tested to date has been genetically stable during the manufacturing in eggs, resulting in vaccine intermediates (MVS and MB) that are genetically identical. These data demonstrate the genetic stability of the virus strains during the manufacturing process and final formulation of the vaccine.

4. Is the same GMO release planned elsewhere in the Community [in conformity with Article 6 (1)], by the same notifier?

Yes ☐	No ☑
If yes, insert the country code(s):	

5. Has the same GMO been notified for release elsewhere in the Community by the same notifier?

Yes ☐	No ☑
If yes: – Member State of notification - Notification number	

6. Has the same GMO been notified for release or placing on the market outside the Community by the same or other notifier?

Yes ☑	No ☐
If yes: – Member State of notification United States 1. FluMist vaccine strains manufactured using the plasmid rescue process has been marketed in the United States since 2008. FluMist® is a trivalent live attenuated influenza vaccine marketed in the United States since 2003 Notification number US Govt. License Number: 1799 2. One clinical study has been conducted with the GMO in adults, MI-CP185. Notification number NCT00860067	

7. Summary of the potential environmental impact of the release of the GMOs

The following characteristics of Q/LAIV have been identified as having the potential to cause adverse effects, listed below, according to the relevant criteria. These effects are equivalent to those arising from the classically-derived (non-GMO) vaccine.

i The vaccine contains live, replication competent virus strains, which leads to recovery of live virus from vaccine recipients for a limited period post-vaccination. The principal potential adverse effect from this characteristic is secondary transmission and infection of unintended human recipients. There has been one documented case of secondary transmission in a study designed to detect transmission among young children (8 to 36 months of age) in a childcare setting during which prolonged close contact is assumed. The calculated risk of transmission was estimated at 0.58% (95% CI 0, 1.7). Therefore this effect can be considered rare. It should also be noted that the one documented case of secondary transmission did not produce signs or symptoms that differed from those of vaccine recipients. Another potential adverse effect arising from this characteristic would be secondary transmission and infection of an animal host. This is considered a theoretical effect in view of the limited host range and replication restriction of the attenuated strains.

The first of these two adverse effects is considered to represent negligible consequences and to have a low likelihood of occurring. The second is considered to represent negligible consequences and to have a negligible likelihood of occurring.

ii The virus strains are attenuated forms of two ubiquitous viruses to which everyone is serially exposed on an annual basis, (influenza A and B). The principal potential adverse effect from this characteristic would be acquisition by vaccine strains of non-attenuated or other potentially pathogenic characteristics. These traits would be identified through control testing prior to release of each product batch. This effect has not been observed despite many clinical and animal studies and remains a theoretical effect.

This adverse effect is considered to represent low or negligible consequences and to have a negligible likelihood of occurring.

Both type A and B virus strains have the potential to reassort with *wt* strains following co-infection and so generate viruses with different combinations of gene segments. To address the possibility of progeny viruses possessing new genotypes due to reassortment of live attenuated influenza vaccine virus and circulating *wt* strains, a study was conducted that applied reverse-genetics to generate 34 reassortant viruses. The results of this study showed that no reassortant strains were more virulent than *wt*, and 33 of the 34 recombinant viruses had less efficient replication than *wt* virus in infected ferrets. This observation is likely due to the fact that each of the 33 reassortants exhibiting reduced efficiency in replication carried at least one gene segment that possessed a known attenuating determinant. The 34th reassortant was a *wt* virus containing the vaccine strain NS gene segment which is not known to confer an attenuation phenotype. This reassortant did not contain any gene segments with a known attenuating phenotype. The results of this study indicate that genetic reassortment between *wt* virus and vaccine strains is not likely to create viruses with new properties compared with either progenitor, and the more likely outcome is that the reassortant will be an attenuated virus. (Parks, 2007)

This adverse effect is considered to represent low or negligible consequences and to have a negligible likelihood of occurring.

B. INFORMATION RELATING TO THE RECIPIENT OR PARENTAL ORGANISMS FROM WHICH THE GMO IS DERIVED

1. Recipient or parental organism characterization:

a) Indicate whether the recipient or parental organism is a:

Viroid	☐
RNA virus	☑
DNA virus	☐
bacterium	☐
fungus	☐
animal	☐
- mammals	☐
- insect	☐
- fish	☐
-other animal	☐ (please specify phylum, class) other, please specify

2. Name

(i) Order and/or higher taxon (for animals) Orthomyxoviridae family
(ii) Genus Influenzavirus A and Influenzavirus B
(iii) Species Influenza A and Influenza B
(iv) Subspecies
(v) Strain A/Ann Arbor/6/60 and B/Ann Arbor/1/66
(vi) pathovar (biotype, ecotype, race, etc.) Not applicable.
(vii) common name Master Donor Virus

3. Geographical distribution of the organism

a) Indigenous to, or otherwise established in Finland:

Yes ☑ No ☐ Not known ☐

b) Indigenous to, or otherwise established in, other EC countries:

(i) Yes ☑

If *yes*, indicate the type of ecosystem in which it is found:

Atlantic ☑
Mediterranean ☑
Arctic ☑
Alpine ☑
Continental ☑

(ii) No ☐

(iii) Not known ☐

c) Is it frequently used in Finland?

Yes ☑ No ☐

d) Is it frequently kept in Finland?

Yes ☑ No ☐

4. Natural habitat of the organism

(a) If the organism is a microorganism

Water ☐
soil, free-living ☐
soil in association with plant-root systems ☐
in association with plant leaf/stem systems ☐
in association with animals ☑

other (specify)

(b) If the organism is an animal: natural habitat or usual agroecosystem:

Not applicable.

5. a) Detection techniques

Given suitable conditions, detection of the MDV (Master Donor Virus) strains requires culture from swabs or by RT-PCR (reverse transcription-polymerase chain reaction to amplify viral RNA

5. b) Identification techniques

The MDV strains may be distinguished from each other and from *wt* influenza strains by genomic sequencing.

6. Is the recipient organism classified under existing Community rules relating to the protection of human health and/or the environment?

Yes ☐	No ☑
	MDV attenuated strains are not listed in Annex III of Directive 2000/54/EC (as amended). However, according to the hazard group classification system, the attenuated strains would meet the criteria for Group 1 (a biological agent that is unlikely to cause human disease).
If yes, specify	

7. Is the recipient organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?

Yes ☐	No ☑	Not known ☐
If yes: a) to which of the following organisms:	humans ☐ animals ☐ plants ☐ other ☐	
b) give the relevant information specified under Annex III A, point II. (A)(11)(d) of Directive 2001/18/EC		

8. Information concerning reproduction

a) Generation time in natural ecosystems:

The recipient organisms (MDV) are live viruses which cannot persist in the environment without a host cell for replication. The viruses are labile, and environmental factors such as sunlight and heat will further diminish their viability. The viruses may persist for hours in dried mucous and may be transmitted by inoculating nasal secretions onto respiratory epithelium. Reproduction is by replication within a specific host cell.

b) Generation time in the ecosystem where the release will take place:

See (8a)

c) Way of reproduction: Sexual ☐ Asexual ☑

d) Factors affecting reproduction:

See (8a)

9. Survivability

a) Ability to form structures enhancing survival or dormancy:

(i) endospores ☐
(ii) cysts ☐
(iii) sclerotia ☐
(iv) asexual spores (fungi) ☐
(v) sexual spores (fungi) ☐
(vi) eggs ☐
(vii) pupae ☐
(viii) larvae ☐

(ix) other, please specify The master donor virus is a live virus and does not form structures

b) Relevant factors affecting survivability:

The viruses are labile and environmental factors such as sunlight and heat will further diminish their viability. The viruses may persist for up to 48 hours on hard surfaces but only survived for <8-12 hours on cloth. Virus transferred from tissues to hands only survived for up to 15 minutes (B. Bean, 1982).

10. a) Ways of dissemination

As with other respiratory viruses, influenza is transmitted through direct contact with infected subjects, airborne droplets, or contaminated surfaces. Infection can occur through the mucous membranes of the eyes, mouth, or nose.

10. b) Factors affecting dissemination

The viruses are labile and environmental factors such as sunlight and heat will further diminish their viability. The virus is also susceptible to common disinfectants.

11. Previous genetic modifications of the recipient or parental organism already notified for release in the country where the notification is made (give notification numbers)

None

C. INFORMATION RELATING TO THE GENETIC MODIFICATION

1. Type of the genetic modification

(i) Insertion of genetic material ☐
(ii) Deletion of genetic material ☐
(iii) Base substitution ☐
(iv) Cell fusion ☐

(v) Other, please specify plasmid rescue method

2. Intended outcome of the genetic modification

The *ca* vaccine strains in Q/LAIV are 6:2 genetic reassortants. In other words, these vaccine strains have 6 gene segments (PB1, PB2, PA, NP, M and NS) from one of two master donor viruses (MDV) and 2 gene segments, haemagglutinin (HA) and neuraminidase (NA) from the *wt* influenza virus. The MDV gene segments of these 6:2 vaccine strains confer the attenuation and replication properties to the vaccines whereas the *wt* gene segments are responsible for eliciting the protective immune responses.

3. a) Has a vector been used in the process of modification?

Yes ☐	No ☑
	The term 'vector' is not relevant for this product. Type A MDV [A/AnnArbor/6/60 (H2N2)], and Type B MDV [B/Ann Arbor/1/66 Clone] were isolated by Dr. H.F. Maassab at the University of Michigan, USA. Q/LAIV vaccine strains are produced from MDVs that were originally derived by cold-adaptation of a type A strain (A/Ann Arbor/6/60 H2N2) and a type B strain (B/Ann Arbor/1/66) by a "cold-adaptation process, consisting of serial passage at sequentially lower temperatures in specific pathogen-free (SPF) primary chick kidney cells. Derivation of the type A master strain, A/Ann Arbor/6/60, the B strain, B/Ann Arbor/1/66.

If no, go straight to question 5.

3. b) <u>If yes, is the vector wholly or partially present in the modified organism</u>?

Yes ☐	No ☐
If no, go straight to question 5.	

4. <u>If the answer to 3 b) is yes, supply the following information</u>

a) Type of vector

plasmid ☐
bacteriophage ☐
virus ☐
cosmid ☐
transposable element ☐

other, please specify

b) Identity of the vector

c) Host range of the vector

d) Presence in the vector of sequences giving a selectable or identifiable phenotype

Yes ☐ No ☐

Antibiotic resistance ☐

Other, specify

Indication of which antibiotic resistance gene is inserted

e) Constituent fragments of the vector

f) Method for introducing the vector into the recipient organism

(i) transformation ☐
(ii) electroporation ☐
(iii) macroinjection ☐
(iv) microinjection ☐
(v) infection ☐

(vi) other, please specify

5. If the answer to question B.3 (a) and (b) is no, what was the method used in the process of modification?

(i) transformation ☐
(ii) microinjection ☐
(iii) microencapsulation ☐
(iv) macroinjection ☐

(v) other, please specify Transfection of plasmid by electroporation to produce vaccine strains, a process called reverse genetics.

6. Information on the insert

a) Composition of the insert

The term 'insert' is not relevant for this product.

Four *wt* influenza strains (from which the NA and HA gene segments are derived) are recommended each year by the WHO, or the EMEA *Ad Hoc* Influenza Working Group, as the basis for vaccines manufacture prior to each annual influenza season, which represent predictions for the most common circulating strains of the forthcoming season.

b) Source of each constituent part of the insert

See 6(a) above

c) Intended function of each constituent part of the insert in the GMO

See 6(a) above.

d) Location of the insert in the host organism

- on a free plasmid ☐
- integrated in the chromosome ☐

- other, please specify

Not applicable.

e) Does the insert contain parts whose product or function are not known?

Yes ☐ No ☑

If yes, please specify

D. INFORMATION ON THE ORGANISM(S) FROM WHICH THE INSERT IS DERIVED (DONOR)

1. Indicate whether it is a:

Viroid	☐
RNA virus	☑
DNA virus	☐
bacterium	☐
fungus	☐
animal	☐
- mammals	☐
- insect	☐
- fish	☐
- other animal	☐ (please specify phylum, class)

other, please specify

Influenza virus, types A and B, Family *Orthomyxoviridae.*

2. Complete name

(i) order and/or higher taxon (for animals)

Orthomyxoviridae family

(ii) family name (for plants)

Not Applicable

(iii) genus

Influenza virus A and Influenza virus B

(iv) species

Influenza A and Influenza B

(v) subspecies

(vi) strain A/H1N1 A/H3N2 B strain of Yamagata lineage B strain of Victoria lineage
(vii) cultivar/breeding line Not Applicable
(viii) pathovar Not Applicable
(ix) common name Influenza

3. <u>Is the organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?</u>

Yes ☑	No ☐	Not known ☐

If *yes*, please specify the following

a) to which of the following organisms?

Humans	☑
animals	☑
plants	☐
other	☐

Wild type influenza strains, types A and B, are well-characterised human pathogens. Influenza A in particular is associated with significant morbidity and mortality.

b) are the donated sequences involved in any way to the pathogenic or harmful properties of the organism?

Yes ☐ No ☑ Not known ☐

The NA and HA antigens are the principal antigens of both type A and B influenza viruses. The NA antigen is a membrane-associated protein that mediates release of virus from the infected cell. The HA antigen is a membrane-associated protein that mediates virus attachment and penetration. Mutations in these antigens permit the virus to evade host immunity due to infection with, or vaccination against, previous seasonal influenza strains. While these antigens are characteristic of pathogenic influenza strains, they do not themselves confer pathogenicity.

If yes, give the relevant information under Annex III A, point II (A), 11(d):

4. <u>Is the donor organism classified under existing Community rules relating to the protection of human health and the environment, such as Directive 90/679/EEC on the protection of workers from risks related to exposure to biological agents at work?</u>

Yes ☑	No ☐
If yes, please specify Wild type influenza A and B viruses are both Group 2 biological agents according to Annex III of Directive 2000/54/EC (as amended).	

5. <u>Do the donor and recipient organism exchange genetic material naturally</u>?

Yes ☑	No ☐	Not known ☐
Both type A and B virus strains have the potential to reassort with *wt* strains following co-infection and could generate viruses with different combinations of gene segments.		

E. INFORMATION RELATING TO THE GENETICALLY MODIFIED ORGANISM

1. Genetic traits and phenotypic characteristics of the recipient or parental organism which have been changed as a result of the genetic modification

a) Is the GMO different from the recipient as far as *survivability* is concerned?

Yes ☐ No ☑ Not known ☐

The GMO is considered equivalent to those described for the MDV strain (recipient organism).

The virus strains used in Q/LAIV, 2 subtype A (ie, A/H1N1 and A/H3N2) and 2 type B, are attenuated (*att*), cold-adapted (*ca*) and temperature sensitive (*ts*) reassortant strains of influenza virus. The *ca* phenotype of the strains allows them to replicate in the upper respiratory passages and the *ts* and *att* phenotypes of the strains largely prevent replication in the lower respiratory tract.

The vaccine strains are 6:2 genetic reassortants. In other words, these vaccine strains have 6 gene segments (PB1, PB2, PA, NP, M and NS) from one of two master donor viruses (MDV) and 2 gene segments, haemagglutinin (HA) and neuraminidase (NA) from the *wt* influenza virus. The MDV gene segments of these 6:2 vaccine strains confer the attenuation and replication properties to the vaccines whereas the *wt* gene segments are responsible for eliciting the protective immune responses.

If yes, please specify

b) Is the GMO in any way different from the recipient as far as mode and/or rate of *reproduction* is concerned?

Yes ☐ No ☑ Not known ☐

c) Is the GMO in any way different from the recipient as far as *dissemination* is concerned?

Yes ☐ No ☑ Not known ☐

If yes, please specify

d) Is the GMO in any way different from the recipient as far as *pathogenicity* is concerned?

Yes ☐ No ☑ Not known ☐

If yes, please specify

2. Genetic stability of the genetically modified organism

The genetic stability of Q/LAIV vaccine strains has been previously demonstrated by evaluating the sequence data collected on 36 different monovalent bulk (MB) lots produced from 10 different MVSs. These data have shown that the nucleotide sequence of the vaccine strains did not vary following either one or two passages in eggs during manufacturing. Every vaccine intermediate tested to date has been genetically stable during the manufacturing in eggs, resulting in vaccine intermediates (including MVS and MB) that are genetically identical. These data demonstrate the genetic stability of the vaccine during the manufacturing process.

Each vaccine strain has been tested in the ferret model to confirm the expected attenuation characteristics. Each of the different vaccine strains has been shown to have the *att* phenotype, and every strain tested has been shown to be attenuated in humans.

3. Is the GMO significantly pathogenic or harmful in any way (including its extracellular products), either living or dead?

Yes ☐ No ☑ Not known ☐

If *yes*,

a) to which of the following organisms?:

humans	☐
animals	☐
plants	☐
other	☐

b) give the relevant information specified under Annex III A, point II (A) (11) (d) and II (C) (2) (i)

4. Description of identification and detection methods

a) Techniques used to detect the GMO in the environment

Given suitable conditions, detection of the Q/LAIV vaccine strains requires culture from swabs or other samples.

b) Techniques used to identify the GMO

The Q/LAIV vaccine strains may be distinguished from each other and from *wt* influenza strains using nucleic acid amplification methods.

F. INFORMATION RELATING TO THE RELEASE

1. Purpose of the release (including any significant potential environmental benefits that may be expected)

Q/LAIV is an intranasally administered, live attenuated quadrivalent influenza vaccine being investigated in a controlled clinical trial for the prevention of disease caused by influenza virus A subtypes and B types by actively immunizing individuals 2 to 18 years of age.

2. Is the site of the release different from the natural habitat or from the ecosystem in which the recipient or parental organism is regularly used, kept or found?

Yes ☐	No ☑
If yes, please specify	

3. Information concerning the release and the surrounding area

a) Geographical location (administrative region and where appropriate grid reference):

The study vaccine will be administered at healthcare facilities where paediatric immunizations are commonly administered.

The following are clinical study sites within Finland where study vaccine will be administered:

Site 1. The GMO will be administered at Kotkan rokotetutkimusklinikka, Karjalantie 10-12, 48600 Kotka, FINLAND
Site 2. The GMO will be administered at Kuopion rokotetutkimusklinikka, Käsityökatu 18, 70100 Kuopio, FINLAND
Site 3. The GMO will be administered at Lahden rokotetutkimusklinikka, Vesijärvenkatu 74, 15140 Lahti, FINLAND
Site 4. The GMO will be administered at Tampereen rokotetutkimusklinikka, Pinninkatu 47, 1. Krs, 33100 Tampere, FINLAND
Site 5. The GMO will be administered at Itä-Vantaan rokotetutkimusklinikka, Asematie 11 A 16, 01300 Vantaa, FINLAND
Site 6. The GMO will be administered at Turun rokotetutkimusklinikkam, Lemminkäisenkatu 14-18 B, 4. Krs, 20520 Turku, FINLAND
Site 7. The GMO will be administered at Kokkolan rokotetutkimusklinikka, Rantakatu 7, 67100 Kokkola, FINLAND
Site 8. The GMO will be administered at Itä-Helsingin rokotetutkimusklinikka, Turunlinnantie 8, 00930 Helsinki, FINLAND
Site 9. The GMO will be administered at Järvenpään rokotetutkimusklinikka, Yhteiskouluntie 17, 04400 Järvenpää, FINLAND
Site 10. The GMO will be administered at Espoon rokotetutkimusklinikka, Keskustorni, 7.

Krs, Tapiontori 1, 02100 Espoo, FINLAND Site 11. The GMO will be administered at Länsi-Vantaan rokotetutkimusklinikka, Jönsaksentie 6 B, 3. Krs, 01600 Vantaa, FINLAND Site 12. The GMO will be administered at Etelä-Helsingin rokotetutkimusklinikka, Vuorikatu 18, 3. Krs, 00100 Helsinki, FINLAND Site 13. The GMO will be administered at Oulun rokotetutkimusklinikka, Kiviharjunlenkki 6, 90220 Oulu, FINLAND Site 14. The GMO will be administered at Porin rokotetutkimusklinikka, Yrjönkatu 23, 4. Krs, 28100 Pori, FINLAND Site 15. The GMO will be administered at Seinäjoen rokotetutkimuskeskus, Keskuskatu 6, 60100 Seinäjoki, FINLAND
b) Size of the site (m^2): (i) actual release site (m^2): Not applicable. (ii) wider release area (m^2): Not applicable.
c) Proximity to internationally recognized biotopes or protected areas (including drinking water reservoirs), which could be affected: The study vaccine will be administered at standard healthcare facilities where paediatric vaccines are commonly administered. It is not anticipated that the study vaccine or any waste associated with study procedures will affect the surrounding ecosystem.
d) Flora and fauna including crops, livestock and migratory species which may potentially interact with the GMO With the exception of ferrets, hamsters and guinea pigs, the Q/LAIV vaccine strains are not capable of establishing an infection in a broad spectrum of animal host species even under controlled conditions. The replication of the vaccine strains was observed in only the upper respiratory tract of ferrets, hamsters and guinea pigs – this demonstrates the expected restriction of replication characteristic of the strains as attenuated virus strains, which is as expected for the host range of these attenuated strains.

4. Method and amount of release

a) Quantities of GMOs to be released: In order to have sufficient investigational product to appropriately distribute to clinical sites in the EU and have sufficient overage to offset any unexpected damaged product (e.g., potential freezer failures at clinical sites), MedImmune estimates that up to a total of 4200 Q/LAIV doses (0.2 ml syringes) and 2800 FluMist doses (0.2 ml syringes) will be imported into the Finland during the course of the study.
b) Duration of the operation: It is anticipated that enrollment of study MI-CP208 will begin in the EU in April 2010 and will be completed by November 2010
c) Methods and procedures to avoid and/or minimize the spread of the GMOs beyond the site of the release Procedures are in place for transport to and from and storage at clinical sites, administration of the vaccine and clinical sample collections, waste handling, and monitoring of viral recovery from study subjects during the trial. These procedures contain the appropriate measures to avoid the spread of the Q/LAIV vaccine in the environment.

5. Short description of average environmental conditions (weather, temperature etc.)

Finland has a climate with warm summers and cold winters.

6. Relevant data regarding previous releases carried out with the same GMO, if any, specially related to the potential environmental and human health impacts from the release

To date, one clinical study with Q/LAIV in Becton Dickinson Accuspray™ (MEDI3250) has been initiated (MI-CP185, A Randomized, Double-Blind, Active Controlled Study to Evaluate the Immunogenicity of MEDI3250 in Adults 18 to 49 Years of Age). This study began enrollment on 23 March 2009, and as of 22 April, all 1800 subjects had been enrolled, and 1798 subjects were dosed. Subjects were randomized 4:1:1 to receive a single intranasal dose of either Q/LAIV-Accuspray, trivalent FluMist containing an influenza B strain from the Yamagata lineage (FluMist-Y Accuspray), or trivalent FluMist containing an influenza B strain from the Victoria lineage (FluMist-V Accuspray).

Based on preliminary safety data for subjects enrolled in study MI-CP185, 6 confirmed SAEs have been reported in 5 subjects (through 30April2009). This study is ongoing, and the data remain blinded so that SAEs cannot be provided by study arm. One subject had an SAE of hypersensitivity that was considered by the investigator to be possibly related to study vaccine.

A second clinical study with Q/LAIV in a Blow-Fill-Seal dosing unit (MEDI8662), MI-CP206, entitled "A Randomized, Partially Blind Active Controlled Study to Evaluate the Immunogenicity of MEDI8662 in Adults 18 to 49 Year of Age" will be conducted in the United States. It is anticipated that enrollment will begin in August 2009 and will be completed by September 2009.

Because Q/LAIV is produced using the same seed viruses and the same manufacturing process that are used to make commercial FluMist ® and the total calculated virus content of Q/LAIV will not exceed the total calculated virus content currently permitted in FluMist (10^8 FFU), the safety profile of Q/LAIV is expected to be similar to that of trivalent FluMist, and the clinical information from studies of FluMist provide data supportive of the safety and efficacy of Q/LAIV.

The safety of FluMist has been extensively documented in clinical and postmarketing studies and in postmarketing surveillance from initial licensure in the United States of the frozen formulation in 2003 (the refrigerated formulation was licensed in 2007) to the current 2008-2009 influenza season. The safety profile of FluMist has been consistent across multiple years, regardless of the strains included in the vaccine. Additionally, FluMist, has been administered at multiple clinical sites in Finland dating back to 1999 in at least 9 previous clinical studies.

Over 6.5 million doses of FluMist manufactured using the plasmid rescue process have been distributed to date. An acceptable safety and tolerability profile has been demonstrated consistently in both paediatric and adult subjects. Solicited (reactogenicity) symptoms and adverse events (AEs) usually consisted of transient upper respiratory and constitutional symptoms. Solicited symptoms are events about which subjects or their parents/legal guardians were specifically queried after vaccination with FluMist. The most common AEs (occurring in ≥ 10% of FluMist subjects and at least 5 percentage points greater than in control) were runny nose or nasal congestion in all ages, fever >100°F in children 2 to 6 years of age, and sore throat in adults.

G. INTERACTIONS OF THE GMO WITH THE ENVIRONMENT AND POTENTIAL IMPACT ON THE ENVIRONMENT, IF SIGNIFICANTLY DIFFERENT FROM THE RECIPIENT OR PARENT ORGANISM

1. Name of target organisms (if applicable)

(i)	order and/or higher taxon (for animals) Primates
(ii)	family name (for plants) Not applicable
(iii)	genus Homo
(iv)	species Homo sapiens
(v)	subspecies Not applicable
(vi)	strain Not applicable
(vii)	cultivar/breeding line Not applicable
(viii)	pathovar Not applicable
(ix)	common name Human

2. Anticipated mechanism and result of interaction between the released GMOs and the target organism (if applicable)

Study subjects will be administered either Q/LAIV vaccine or FluMist intranasally. The mechanism of action of Q/LAIV is to mimic the immunologic responses of natural infection by replication in the nasal passages.

3. Any other potentially significant interactions with other organisms in the environment

None.

4. Is post-release selection such as increased competitiveness, increased invasiveness for the GMO likely to occur?

Yes ☐	No ☑	Not known ☐

5. Types of ecosystems to which the GMO could be disseminated from the site of release and in which it could become established

Q/LAIV is labile and does not survive outside of a host cell at room temperature for more than 48 hours on hard surfaces and only <8-12 hours on cloth (B. Bean, 1982). The study will be conducted at standard healthcare facilities and administration will be performed intranasally directly into the study subject. It is therefore not anticipated that the study vaccine or any waste associated with study procedures will be distributed to or affect the surrounding ecosystem.

6. Complete name of non-target organisms which (taking into account the nature of the receiving environment) may be unintentionally significantly harmed by the release of the GMO

(i) order and/or higher taxon (for animals) None
(ii) family name (for plants) None
(iii) genus None
iv) species None
(v) subspecies None
(vi) strain None
(vii) cultivar/breeding line None
(viii) pathovar None
(ix) common name None

7. Likelihood of genetic exchange in vivo

a) from the GMO to other organisms in the release ecosystem: Both type A and B virus strains have the potential to reassort with *wt* strains following co-infection and so generate viruses with different combinations of gene segments. The principal potential adverse effect from this characteristic would be reassortment to generate a novel strain with non-attenuated or other potentially pathogenic characteristics.
b) from other organisms to the GMO: See 7(a) above

c) likely consequences of gene transfer:

See 7(a) above

8. Give references to relevant results (if available) from studies of the behaviour and characteristics of the GMO and its ecological impact carried out in simulated natural environments (e.g. microcosms, etc.):

No studies have been conducted on the ecological impact of Q/LAIV on simulated natural environments.

9. Possible environmentally significant interactions with biogeochemical processes (if different from the recipient or parental organism)

There is no evidence to suggest that Q/LAIV will have any impact on agricultural production, general ecology, environmental quality and pollution in the area of release. Q/LAIV is not an agriculture genetically modified organism. It is an RNA animal virus that replicates in mammalian cells. Q/LAIV cannot infect microbes and plant cells. Q/LAIV does not persist in the environment. It can only remain infectious outside a host cell for no more than 48 hours on hard surfaces and only <8-12 hours on cloth (B. Bean, 1982). It is rapidly inactivated by UV, heat and pH changes. It is susceptible to common disinfectants and cleaning agent, such as 1% sodium hypochlorite, 70% ethanol, 2% glutaraldehyde and detergents.

H. INFORMATION RELATING TO MONITORING

1. Methods for monitoring the GMOs

The study will be monitored by MedImmune or its designee on a regular basis throughout the study period in accordance with general monitoring principles set forth in ICH E5. Safety of the study subjects, including monitoring for influenza enhanced disease, will be evaluated throughout the duration of the study. Immune response to the Q/LAIV vaccine will be assessed during the study.

2. Methods for monitoring ecosystem effects

The dissemination and impact of Q/LAIV on ecosystems is limited because dissemination requires close contact with infected nasal secretions. The study will be conducted at standard healthcare facilities where paediatric vaccines are normally administered. It is not anticipated that the study vaccine or any waste associated with study procedures will affect the surrounding ecosystem; therefore monitoring of ecosystem effects is not planned. Q/LAIV is a Biosafety Level 1 organism according to guidelines published by the United States Centers for Disease Control and Prevention (CDC), and is therefore considered to have minimal potential hazard to laboratory personnel and the environment. Standard universal precautions that are mandated in medical facilities are adequate to prevent accidental transmission.

3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms

As noted previously, there is minimal risk of gene exchange between circulating wild-type and vaccine viruses. Additionally, Q/LAIV replication and survival is reliant on appropriate host organisms. Therefore, no monitoring of other organisms is planned.

4. Size of the monitoring area (m^2)

Not applicable.

5. Duration of the monitoring

Subjects will be followed from administration of study vaccine through 180 days after the final dose of vaccine.

6. Frequency of the monitoring

Frequency of monitoring for safety, immunogenicity is detailed within the study protocol.

I. INFORMATION ON POST-RELEASE AND WASTE TREATMENT

1. Post-release treatment of the site

Clinical study sites will be instructed to follow normal site procedures for disposal of biomedical waste.

2. Post-release treatment of the GMOs

All unused study vaccine will be returned to MedImmune's central storage depot in the United Kingdom or disposed of at the clinical site upon authorization of MedImmune. Q/LAIV should be discarded as "biohazardous waste (a.k.a. "medical waste") or, alternatively, decontamination of waste can be performed by steam sterilization for 30 minutes at 121°C.

3. a) Type and amount of waste generated

Up to approximately 2100 0.2 ml dose of Q/LAIV and 1400 0.2 ml dose FluMist could be generated as waste. All unused study vaccine will be returned to MedImmune's central storage depot in the United Kingdom or disposed of at the clinical site upon authorization of MedImmune.

3. b) Treatment of waste

Q/LAIV is susceptible to common disinfectants (e.g., 1% sodium hypochlorite, 70% ethanol, 2 % glutaraldehyde) and is inactivated by UV radiation and steam sterilization. Both used and unused dosing units to be discarded should be handled as "biohazardous waste" (a.k.a. medical waste) and stored in appropriately labelled sealed containers until they can be reconciled by the site Clinical Research Associate (CRA). They can then be destroyed according to site procedures for biohazardous waste.

J. INFORMATION ON EMERGENCY RESPONSE PLANS

1. Methods and procedures for controlling the dissemination of the GMO(s) in case of unexpected spread

Unexpected spread of Q/LAIV would be limited to accidental release contents (0.2 ml total); therefore, possibility of spread would be minimal. Q/LAIV is susceptible to common disinfectants and physical inactivation is rapidly achieved by UV irradiation and steam sterilization. Q/LAIV does not survive outside of a host at room temperature for more than 48 hours on hard surfaces and only survived for <8-12 hours on cloth (B. Bean, 1982).

2. Methods for removal of the GMO(s) of the areas potentially affected

If decontamination procedures are deemed necessary for any reason, a freshly prepared 1:10 solution of household bleach (~3.5% sodium hypochlorite) and water can be used.

3. Methods for disposal or sanitation of plants, animals, soils etc. that could be exposed during or after the spread

Administration of Q/LAIV will occur only within contained clinical sites. It is therefore not anticipated that Q/LAIV will come into direct contact with any plants, animals or soils.

4. Plans for protecting human health and the environment in the event of an undesirable effect

As described above, extensive procedural controls are in place for the transport, storage, administration, disposal and monitoring of Q/LAIV vaccination for the duration of the clinical study. Should any unexpected undesirable effect occur, MedImmune will follow standard procedures of assessment of the effect and decisions regarding study continuance.