Summary Notification Information Format
(referred to in art. 11 of Directive 2001/18/EC)

in accordance with the Council Decision 2002/813/EC

presented by the Merial Laboratories

for the vaccine M725 (R) containing vCP65 GMO

for its deliberate release
(clinical trials)
PART 1 (COUNCIL DECISION 2002/813/EC)

SUMMARY NOTIFICATION INFORMATION FORMAT FOR THE RELEASE OF GENETICALLY MODIFIED ORGANISMS OTHER THAN HIGHER PLANTS IN ACCORDANCE WITH ARTICLE 11 OF DIRECTIVE 2001/18/EC

In order to tick one or several possibilities, please use crosses (meaning x or X) into the space provided as (.)

A. General information

1. Details of notification

(a) Member State of notification: France
(b) Notification number: B/FR/06/03/02
(c) Date of acknowledgement of notification: 20/02/2006
(d) Title of the project

Development of a vaccine against feline rabies. Experiment outside containment (clinical trial) for the study of the safety and the efficacy of a subcutaneous administration of a recombinant canarypoxvirus expressing the surface glycoprotein G gene from Rabies virus (vCP65).

(e) Proposed period of release: From May 2006 to December 2006

2. Notifier

Name of institution or company: Merial, 29 avenue Tony Garnier 69007 Lyon France

3. GMO characterisation

(a) Indicate whether the GMO is a:

- viroid ()
- RNA virus ()
- DNA virus X
- bacterium ()
- fungus ()
- animal
  - mammals ()
  - insect ()
  - fish ()
  - other animal ()

specify phylum, class …
(b) Identity of the GMO (genus and species)

vCP65 consisting of a recombinant canarypox virus expressing the surface glycoprotein G gene from Rabies virus, under control of the H6 promoter from the vaccinia virus.

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

Recombinant virus vCP65 was subjected to sequential passages (from pre-master seed to production level, i.e. X-1 to X+5) in chicken embryo fibroblasts. The surface expression analysis of the rabies glycoprotein was performed by immunoscreen using a monoclonal antibody and shown to be stable on passages.

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

   Yes (.)  No  X

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  X

If yes:

- Member State of notification …
- Notification number B/../../…

Please use the following country codes:

Austria AT; Belgium BE; Germany DE; Denmark DK; Spain ES; Finland FI; France FR; United Kingdom GB; Greece GR; Ireland IE; Iceland IS; Italy IT; Luxembourg LU; Netherlands NL; Norway NO; Portugal PT; Sweden SE

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

   Yes  X  No (.)

If yes:

- Member State of notification United States of America

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

<table>
<thead>
<tr>
<th>Consequence of hazard</th>
<th>Likelihood of hazard occurring</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Severe</td>
<td>High</td>
</tr>
<tr>
<td>Medium</td>
<td>High</td>
</tr>
<tr>
<td>Low</td>
<td>Medium/low</td>
</tr>
<tr>
<td>Negligible</td>
<td>Effectively zero</td>
</tr>
</tbody>
</table>

The overall risk for environment is defined as effectively zero.
B. Information relating to the recipient or parental organism from which the GMO is derived

1. Recipient or parental organism characterisation:

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

(select one only)

viroid (.)
RNA virus (.)
DNA virus X
bacterium (.)
fungus (.)
animal
- mammals (.)
- insect (.)
- fish (.)
- other animal (.)
  (specify phylum, class) …
other, specify …

2. Name

(i) order and/or higher taxon (for animals) Virus
(ii) genus Avipoxvirus
(iii) species Canarypox virus
(iv) subspecies -
(v) strain ALVAC clone
(vi) pathovar (biotype, ecotype, race, etc.) -
(vii) common name strain of the KANAPOX vaccine (live vaccine against canary pox)

3. Geographical distribution of the organism

(a) Indigenous to, or otherwise established in, the country where the notification is made:
Yes X No (.) Not known (.)
(Wild strain (canary pox) and vaccine strain (of KANAPOX, live vaccine against canary pox registered in France)
(b) Indigenous to, or otherwise established in, other EC countries:
   (i) Yes X
(Wild strain (canary pox) and vaccine strain (of KANAPOX, live vaccine against canary pox)

If yes, indicate the type of ecosystem in which it is found: Not applicable

Atlantic ..
Mediterranean ..
Boreal ..
Alpine ..
Continental ..
Macaronesian ..

(ii) No (.)
(iii) Not known (.)

(c) Is it frequently used in the country where the notification is made?
   Yes X No (.)
(the KANAPOX vaccine is manufactured in France)

(d) Is it frequently kept in the country where the notification is made?
   Yes X 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 (.)
   other, specify during infection in an animal (canary)

(b) If the organism is an animal: natural habitat or usual agroecosystem: Not applicable

5. (a) Detection techniques
Culture on CEC (chick embryo cells) and microscopy

(b) Identification techniques
Restriction endonuclease mapping of the viral DNA
IFI
PCR, probe possible
Western blot
6. Is the recipient organism classified under existing Community rules relating to the protection of human health and/or the environment?
   Yes X  No (.)
If yes, specify
Group I, Class 1. Commission of Genetic engineering (France)

It should be noted that the organism has been classified at the BL-1 level by the Advisory Commission of the NIH. (“Agenda item XXIV” at the meeting of the “recombinant DNA Advisory Committee (RAC) of 7-8 June 1993).

7. Is the recipient organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?
   Yes (.)  No  X (it is a vaccine strain)  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:
       Not applicable

   (b) Generation time in the ecosystem where the release will take place:
       Not applicable

   (c) Way of reproduction: Not applicable Sexual . Asexual

   (c) Factors affecting reproduction:
       Viral type cytoplasmic replication in permissive cells (canary, CEC)
9. Survivability
Not applicable

(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, specify …

(b) relevant factors affecting survivability:

10. (a) Ways of dissemination
Contact or airbone dissemination (for the wild strain)
Very limited dissemination for the vaccine strain

(b) Factors affecting dissemination
High density of canary population kept in cages

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)
…, B/../../../…

The recipient virus is not a genetically modified virus by itself (the wild strain has been attenuated by more than 200 passages on CEC). The obtained strain has been passaged four times on CEC (4th passage is called strain CP1). After four cloning cycles by isolation on plaque (plaque cloning), this clone has been called "ALVAC".

Various projects have used the ALVAC clone as a recipient:

<table>
<thead>
<tr>
<th>Identity of recombinant virus</th>
<th>Origin of the insert</th>
<th>Target species</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>vCP65</td>
<td>Rabies virus</td>
<td>Cat</td>
<td>Registered in the USA (USDA/APHIS)</td>
</tr>
<tr>
<td>vCP258</td>
<td>Canine distemper virus</td>
<td>Dog, ferret</td>
<td>Registered in the USA (USDA/APHIS)</td>
</tr>
<tr>
<td>vCP97</td>
<td>Feline leukemia virus</td>
<td>Cat</td>
<td>Registered in the EC (centralised procedure, MA EU/2/00/019/001-003 and EU/2/00/019/004-007) and USA (USDA/APHIS)</td>
</tr>
<tr>
<td>vCP1529, vCP1533</td>
<td>Equine Influenza A (Kentucky and Newmarket strains)</td>
<td>Horse</td>
<td>Registered in the EC (centralised procedure, MA EU/2/03/037/001-005) and EU/2/03/038/001-005)</td>
</tr>
<tr>
<td>vCP2017</td>
<td>West Nile virus</td>
<td>Horse</td>
<td>Registered in the USA (USDA/APHIS)</td>
</tr>
</tbody>
</table>
C. **Information relating to the genetic modification**

1. **Type of the genetic modification**
   - (i) insertion of genetic material X
   - (ii) deletion of genetic material X
   - (iii) base substitution ()
   - (iv) cell fusion ()
   - (v) others, specify …

2. **Intended outcome of the genetic modification**
   Insertions of a cassette containing the rabies glycoprotein G gene under control of the vaccinia-derived H6 promoter for expression and, subsequently, deletion of the canarypox virus gene selected to be the site of insertion (i.e. C5)

3. (a) **Has a vector been used in the process of modification?**
   - Yes X  No ()
   
   If no, go straight to question 5.

   (b) **If yes, is the vector wholly or partially present in the modified organism?**
   - Yes X  No ()
   
   If no, go straight to question 5.

4. **If the answer to 3(b) is yes, supply the following information**
   - (a) **Type of vector**
     - plasmid X
     - bacteriophage ()
     - virus ()
     - cosmid ()
     - transposable element ()
     - other, specify …

   - (b) **Identity of the vector**
     - pRW838

   - (c) **Host range of the vector**
     - *Escherichia coli*

   - (d) **Presence in the vector of sequences giving a selectable or identifiable phenotype**
     - Yes (.)  No X
     
     antibiotic resistance (.)
     
     other, specify …

   Indication of which antibiotic resistance gene is inserted …
(e) Constituent fragments of the vector
prW838 = pUC9 + flanking arm C5L + H6 promoter + Glycoprotein G gene + flanking arm C5R

(f) Method for introducing the vector into the recipient organism

(i) transformation (.)
(ii) electroporation (.)
(iii) macroinjection (.)
(iv) microinjection (.)
(v) infection (.)
(vi) other, specify X


5. If the answer to question B.3(a) and (b) is no, what was the method used in the process of modification?
Not applicable

(i) transformation (.)
(ii) microinjection (.)
(iii) microencapsulation (.)
(iv) macroinjection (.)
(v) other, specify ...

6. Composition of the insert

(a) Composition of the insert
The insert is constituted of an expression cassette (glycoprotein G gene under control of vaccinia virus H6 promoter) surrounded by flanking arms of canarypox virus origin.

(b) Source of each constituent part of the insert
Expressed gene:
Glycoprotein G gene from rabies virus

Promoter:

Flanking arms:
ALVAC origin

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

Flanking arms: for the homologous recombination
Promoter: for the specific expression of the gene
Gene: expression of the protective immunogen
(d) Location of the insert in the host organism
- on a free plasmid (.)
- integrated in the chromosome (.)
- other, specify X
    integrated into the viral genome

(e) Does the insert contain parts whose product or function are not known?
Yes (.) No X
If yes, specify …

D. Information on the organism(s) from which the insert is derived

For the H6 promoter:

1. Indicate whether it is a:
   viroid (.)
   RNA virus (.)
   DNA virus X
   bacterium (.)
   fungus (.)
   animal
     - mammals (.)
     - insect (.)
     - fish (.)
     - other animal (.)
     (specify phylum, class) …
   other, specify …

2. Complete name
   (i) order and/or higher taxon (for animals) Virus
   (ii) family name for plants Poxviridae
       subfamily: Chordopoxviridae
   (iii) genus Orthopoxvirus
   (iv) species Vaccinia
   (v) subspecies -
   (vi) strain -
   (vii) cultivar/breeding line -
   (viii) pathovar -
   (ix) common name Vaccinia virus

3. Is the organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?
   Yes (.) No X (vaccine strain) Not known (.)
   If yes, specify the following:
(b) to which of the following organisms:

- humans (.)
- animals (.)
- plants (.)
- other ..

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

Yes (.)
No (.)
Not known (.)

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

4. 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 to exposure to biological agents at work?

Yes X
No (.)

If yes, specify class 3

5. Do the donor and recipient organism exchange genetic material naturally?

Yes (.)
No X
Not known (.)

For the inserted sequence (glycoprotein G gene):

1. Indicate whether it is a:

- viroid (.)
- RNA virus X
- DNA virus (.)
- bacterium (.)
- fungus (.)
- animal
  - mammals (.)
  - insect (.)
  - fish (.)
  - other animal (.)
  (specify phylum, class) ...
- other, specify ...

Merial
February 2006
AT/RMM/EBR.06.D33
2. Complete name

(j) order and/or higher taxon (for animals)     Virus
(ii) family name for plants                    Rhabdoviridae
(iii) genus                                  Lyssavirus
(iv) species                                 -
(v) subspecies                               -
(vi) strain                                  Era
(vii) cultivar/breeding line                 -
(viii) pathovar                               -
(ix) common name                              Rabies virus

3. Is the organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?
   Yes X  No (.)  Not known (.)
   If yes, specify the following:
   
   (c) to which of the following organisms:

       humans     X
       animals    X
       plants     (.)
       other      ..

   (b) are the donated sequences involved in any way to the pathogenic or harmful properties of the organism
   Yes X)  No (.)  Not known (.)
   If yes, give the relevant information under Annex III A, point II(A)(11)(d):
   In fact the glycoprotein G (gG) gene encodes a surface glycoprotein G which is the basic unit of the surface projections of the rabies virus. Therefore, the gG gene product is neither toxic nor pathologic in and of itself.

4. 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 to exposure to biological agents at work?
   Yes X  No (.)
   If yes, specify  class 3

5. Do the donor and recipient organism exchange genetic material naturally?
   Yes (.)  No X  Not known (.)

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 X  Not known (.)
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 X  Unknown (.)
Specify …

(d) is the GMO in any way different from the recipient as far as dissemination is concerned?
   Yes (.)  No X  Not known (.)
Specify …

(e) is the GMO in any way different from the recipient as far as pathogenicity is concerned?
   Yes (.)  No X  Not known (.)
Specify …

2. Genetic stability of the genetically modified organism
   Recombinant virus vCP65 was subjected to sequential passages (from pre-master seed to production level, *i.e.* X-1 to X+5) in chicken embryo fibroblasts. The surface expression analysis of the rabies glycoprotein was performed by immunoscreen using a monoclonal antibody and shown to be stable on passages.

3. Is the GMO significantly pathogenic or harmful in any way (including its extracellular products), either living or dead?
   Yes (.)  No X  Unknown (.)

   (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
       Isolation on CEC (by culture) and microscopy
(b) Techniques used to identify the GMO
Restriction endonuclease mapping of the viral DNA
IFI
PCR, probe possible
Western blot

F. Information relating to the release

1. Purpose of the release (including any significant potential environmental benefits that may be expected)
   Study of the safety and the efficacy of the vaccine containing the GMO in target species (cats).

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 X No (.)
   If yes, specify …
   The GMO is injected to cats (non-permissive species, does not generally allow the replication of avipoxvirus and the canarypox virus in particular).

3. Information concerning the release and the surrounding area

   (a) Geographical location (administrative region and where appropriate grid reference):
       French departments: Bouches-du-Rhône (13), Côte-d’Or (21), Drôme (26), Gard (30), Haute-Garonne (31), Gironde (33), Isère (38), Loire-Atlantique (44), Maine-et-Loire (49), Morbihan (56), Pyrénées-Orientales (66), Rhône (69), Haute-Savoie (74), Yvelines (78), Tarn (81), Vaucluse (84), Haute-Vienne (87), Val-de-Marne (94)

   (b) Size of the site (m$^2$):
       … m$^2$
       41 veterinary practices

       (i) actual release site (m$^2$):
           … m$^2$
       (ii) wider release site (m$^2$):
           … m$^2$

   (c) Proximity to internationally recognised biotopes or protected areas (including drinking water reservoirs), which could be affected:
       Not applicable (non-diffusible virus)

   (d) Flora and fauna including crops, livestock and migratory species which may potentially interact with the GMO
       None

4. Method and amount of release

   (a) Quantities of GMOs to be released:
       One dose (maximum titre 7.8log$_{10}$ CCID50 per dose) will be administered to each cat included in the trial
(b) Duration of the operation:
Each cat is administered one injection of vCP65. The trial will last 7 months.

(c) Methods and procedures to avoid and/or minimise the spread of the GMOs beyond the site of the release
- subcutaneous parenteral injection (natural physical containment)
- non-permissive species (natural biological containment)
- recovery of contaminated containers and materials (destruction by incineration).

5. Short description of average environmental conditions (weather, temperature, etc.)
Release for field trial in France. Environmental conditions (weather, temperature, etc.) should not affect survival, multiplication and dissemination.

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.
Several millions of doses of vCP65 have been used in the USA and in Canada since end of 1998 without problems related to the GMO nature of the vaccine.

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 organism (if applicable)
  (i) order and/or higher taxon (for animals)
  Kingdom: Animal
  Phylum: Vertebrates
  Class: Mammals
  Subclass:...
  Superorder:...
  Order: Carnivores
  Suborder:...
  (ii) family name for plants
  (iii) genus...
  (iv) species
  (v) subspecies...
  (vi) strain...
  (vii) cultivar/breeding line...
  (viii) pathovar...
  (ix) common name
  Cat

2. Anticipated mechanism and result of interaction between the released GMOs and the target organism (if applicable)
Expression of the inserted gene, without replication of the GMOs, leading to the development of a specific protective immunity.

3. Any other potentially significant interactions with other organisms in the environment
Expression without replication in mammals, non pathogenic in permissive species (canary type), the strain being a widely used vaccine strain (more than 1.4 million canaries vaccinated at this day).
4. Is post-release selection such as increased competitiveness, increased invasiveness for the GMO likely to occur?
   Yes (.)  No  X  Not known  (.)
   Give details
   ...

5. Types of ecosystems to which the GMO could be disseminated from the site of release and in which it could become established
   Within the scope of the experimental protocol, there is no such risk.

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
   Not applicable. Non-pathogenic vaccine strain.

   (i) order and/or higher taxon (for animals)  ...
   (ii) family name for plants  ...
   (iii) genus  ...
   (iv) species  ...
   (v) subspecies  ...
   (vi) strain  ...
   (vii) cultivar/breeding line  ...
   (viii) pathovar  ...
   (ix) common name  ...

7. Likelihood of genetic exchange in vivo
   (a) from the GMO to other organisms in the release ecosystem:
       see b)

   (b) from other organisms to the GMO:
       Potential for genetic transfer and exchange between poxviruses:
       only the recombination between the ALVAC vector or ALVAC-derived recombinants (such as the GMO) and another poxvirus is theoretically possible. The construction of the GMO itself is based upon an in vitro homologous recombination. However, for an in vivo recombination in natural conditions, a simultaneous co-infection in the same cell by two poxviruses (one of them being the ALVAC vector or the ALVAC-derived recombinant) with some degree of homology is necessary. This is highly unlikely to happen in the conditions of dissemination.

       Potential for genetic transfer and exchange with a virus related to the donor organism:
       recombination between a canarypox virus (DNA virus) and a rabies virus (RNA virus) is highly unlikely to happen because of the different nature of the nucleic acids. In addition, canarypox and rabies viruses do not infect the same cells.

       In conclusion, likelihood of genetic transfer and exchange in vivo involving the GMO with other organisms is highly unlikely.

   (c) likely consequences of gene transfer:
       Not applicable (gene transfer is highly unlikely, see b.).
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 stimulated natural environments (e.g. microcosms, etc.):

Studies on the GMO:
*In vitro*, the lack of replication of the GMO in mammalian cells (of cat or dog origin) was demonstrated.
*In vivo*, safety was demonstrated in cats, mice and guinea-pigs. Absence of shedding was demonstrated in cats. In canary birds, its safety was equivalent to that of CPpp parental strain at the systemic and local levels.

In addition, several millions of doses of vCP65 have been used in the USA and in Canada without problems related to the GMO nature of the vaccine.

Studies on the ALVAC vector:
Studies in men, horses, cats, dogs, cattle, pigs, mice, guinea-pigs, rabbits, monkeys as well as in cyclophosphamid e immuno-depressed mice have demonstrated the safety of this virus. Also, the impossibility of replication of the vector in mammals has been demonstrated *in vitro* on mammalian cells (equine, canine and feline) and evaluated in the mouse using an ALVAC luciferase construct.

9. Possible environmentally significant interactions with biogeochemical processes (if different from the recipient or parental organism)
Not applicable.

H. Information relating to monitoring

1. Methods for monitoring the GMOs
   The GMO may be isolated by culture on CEC (test for cytopathic effect and characterisation by indirect immunofluorescence). The GMO is a non replicative organism which disappears rapidly after parenteral injection. This method of monitoring will be used if necessary.

2. Methods for monitoring ecosystem effects
   The animals which are administered the GMO are individually identified and are monitored by a veterinarian. Both the veterinarian and the owner are informed about the nature of the GMO. The protocol contains a description of the monitoring and data system concerning the animal and its immediate environment.

3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms
   Not applicable.

4. Size of the monitoring area (m²)
   Practice of 41 veterinarians located in various departments of France.

5. Duration of the monitoring
   The trial will last 7 months (each animal is monitored for at least 4 weeks after the vaccine injection)
6. Frequency of the monitoring
Each animal is administered one injection after a clinical examination. The injection, the blood samples and the reading of abnormal reactions immediately after vaccination are performed by a veterinarian investigator (responsible for the implementation of the trial for Merial).

The post vaccinal monitoring is conducted by the owner and by the veterinarian investigator. The owner, fully informed on the nature of the GMO may contact the veterinarian investigator at all time. The veterinarian monitor (responsible for the monitoring of trials for Merial) is systematically informed when an abnormal reaction (i.e. that can not be considered as a classical reaction to vaccination) occurs.

I. Information on post-release and waste treatment

1. Post-release treatment of the site
Not applicable. The virus is injected by parenteral route (physical containment).

2. Post-release treatment of the GMOs
Not applicable. The virus disappears rapidly (because of biological and physical containments).

3. (a) Type and amount of waste generated
Glass bottle (one per cat) and material for injection (needle, syringe)

(b) Treatment of waste
Waste will be recovered, then destroyed by incineration under the responsibility of Merial.

J. Information on emergency response plans

1. Methods and procedures for controlling the dissemination of the GMO(s) in case of unexpected spread
The host range of the canarypox is very narrow and only canaries could be affected by an epidemic caused by the canarypox virus. The transmission between canaries requires a close contact (same or contiguous cages). In this case, classical isolation and disinfection measures would be implemented.

Canarypoxvirus does not spread among chickens and does not replicate in mammals.

2. Methods for removal of the GMO(s) of the areas potentially affected
In case of accident (broken bottles) or accidental contamination of surfaces, disinfection is carried out with bleach. In case of contamination of the skin of the animal or persons in charge of its restrain during the injection, the contaminated area will be treated, as the injection site, with classical disinfectants (70° ethanol solution, bleach).

3. Methods for disposal or sanitation of plants, animals, soils, etc. that could be exposed during or after the spread
Not applicable.
4. Plans for protecting human health and the environment in the event of an undesirable effect

In case of accidental injection to man, a physician will be notified for monitoring, if necessary. Indeed, the ALVAC vector by itself or as recombinant has already been used in humans (trials, at the phase I and II) without observing any safety problem, even after several administrations. Because the GMO and the vector were proven to be safe (non replicative in mammals) and because there were no pathogenic effects caused by the products expressed by the GMO, only a medical data system (human and veterinary) will be implemented. In all cases, the person responsible for the trial will be informed. All events will be recorded and analysed in detail as well as their monitoring if any.

In case of adverse effects, three phases are differentiated as follows in chronological order:

- Alert phase:
  . any observation which cannot be related to the normal post-vaccinal adverse reactions (transient and mild swelling at the injection site and transient lethargy) must be reported to the investigator veterinary surgeon and to the monitor of the trial.
  . the concerned animal will be kept indoors by its owner.

- Investigation phase:
  . appropriate samples are collected and sent to the laboratory for virus isolation and identification,
  . treatment of the animal is immediately prescribed by the veterinary surgeon.

- Action phase:
  . the diagnosis is known before the end of the trial and the event is not related to the vaccine: the investigator starts treating the concerned animal.
  . the diagnosis is known before the end of the trial and the event is related to the vaccine: the recruitment of cats for the trial is stopped. Owners of cats which have already been vaccinated with the vCP65 vaccine are asked to keep their cats isolated for a 1-month follow-up.
  . the cause of the event is not known by the end of the trial:
    If the cause of the unexpected event is not established at the end of the trial, an adverse reaction related to the vaccine cannot be eliminated. The follow-up of all the animals included in the trial will be extended for 1 month after the end of the trial.