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	The Netherlands
(b)	Notification number	B/NL/03/05
(c)	Date of acknowledgement of notification	29/08/2003
(d)	Title of the project	A double-blind, randomized, placebo controlled dose-escalating phase 1 study to evaluate the safety and immunogenicity of a MVA HIV-1 vaccine administered by three different routes and at three different dosage levels in HIV-uninfected healthy volunteers at lower risk of infection.
(e)	Proposed period of release	February 2004-February 2005

2. Notifier

Name of institution or company: ***International AIDS Vaccine Initiative, New York, USA.***

3. GMO characterization

(a) Indicate whether the GMO is a:

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

specify phylum, class ***POXVIRIDAE***

(b) Identity of the GMO (genus and species)
Modified vaccinia virus Ankara-based anti-HIV vaccine (MVA.HIVA)

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

4. Is the same GMO release planned elsewhere in the Community (in conformity with Article 6(1)), by the same notifier?
Yes **(X)** No (.)
If yes, insert the country code(s) ***GB***

5. Has the same GMO been notified for release elsewhere in the Community by the same notifier?
Yes **(X)** No (.)
If yes:
- Member State of notification **GB**
- 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 ***Switzerland, South Africa, Kenya, Uganda***
- Notification number ***Trial 2003GT1001***

7. Summary of the potential environmental impact of the release of the GMOs.
NONE

B. Information relating to the recipient or parental organism from which the GMO is derived

1. Recipient or parental organism characterization:

(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) ***POXVIRUS***

other, specify …

2. Name

(i)	order and/or higher taxon (for animals)	***Poxviridae***
(ii)	genus	***Orthopoxvirus***
(iii)	species	***Vaccinia virus(Cowpox)***
(iv)	subspecies	…
(v)	strain	…
(vi)	pathovar (biotype, ecotype, race, etc.)	…
(vii)	common name	***Modified vaccinia virus Ankara***

3. Geographical distribution of the organism

(a) Indigenous to, or otherwise established in, the country where the notification is made:
Yes (.) No (.) Not known (***X***)

(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	..
Mediteranean	..
Boreal	..
Alpine	..
Continental	..
Macaronesian	..

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

(c) Is it frequently used in the country where the notification is made?
Yes () No (.) ***N/A***

(d) Is it frequently kept in the country where the notification is made?
Yes () No (.) ***N/A***

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: ***"No natural host known, current virus derived from cowpox, gradually transformed as a result of person to person vaccination"*** (Mendell, Douglas, Bennett : Principles and Practices in Infectious Diseases)

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

5. (a) Detection techniques
(b) Identification techniques

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
Vaccine against smallpox (BSL 1)

7. Is the recipient organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?
Yes (.) No (***X***) 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:
…
(b) Generation time in the ecosystem where the release will take place:
…
(c) Way of reproduction: Sexual .. Asexual ..

(c) Factors affecting reproduction:

MVA was derived from the vaccinia strain Ankara by more than 570 serial passages in primary chick embryo fibroblasts, which severely compromised its capacity to replicate in mammalian cells (Mayr et al, 1975; 1998).

9. Survivability
(a) ability to form structures enhancing survival or dormancy:

(i)	endospores	(.)
(ii)	cysts	(.)
(iii)	sclerotia	(.)
(iv)	asexual spores (fungi)	(.)
(v)	sexual spores (funghi)	(.)
(vi)	eggs	(.)
(vii)	pupae	(.)
(viii)	larvae	(.)
(ix)	other, specify …	

(b) relevant factors affecting survivability:
…

10. (a) Ways of dissemination
…

(b) Factors affecting dissemination

MVA is incapable of replication in humans and thus there should be no virus shedding from the vaccinated individuals.

The genetically modified viral vaccine is not able to survive, disseminate in and/or displace other organisms and is not pathogenic to animals or plants

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/../../…

C. **Information relating to the genetic modification**

1. Type of the genetic modification

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

2. Intended outcome of the genetic modification

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 (.) No (**X**)

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	(.)
bacteriophage	(.)
virus	(.)
cosmid	(.)
transposable element	(.)
other, 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, 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, specify	…

6. Composition of the insert

(a) Composition of the insert

The vaccine construct was prepared by recombination in vitro between non-recombinant MVA cultured in Chicken Embryo Fibroblasts cells and a shuttle vector containing the HIVA coding sequence plus a selectable marker gene (β-galactosidase) to allow identification of recombinants.

The HIVA sequence (insert) is 1602 bp in length and encodes only HIV-1 gag (structural) protein and a series of overlapping epitopes (8-10 amino acids long) from the HIV-1 gag, pol, nef and env proteins.

(b) Source of each constituent part of the insert
Synthetic
Commercial plasmid

(c) Intended function of each constituent part of the insert in the GMO
HIVA : immunoprotection against HIV infection
(β-galactosidase): detection of recombinant product

(d) Location of the insert in the host organism

- on a free plasmid (.)
- integrated in the chromosome (**X**)
- other, specify …

(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 : *Human Immunodeficiency Virus-1 Clade A* (but insert is of synthetic origin)

1. Indicate whether it is a:

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

(specify phylum, class) ***Retroviridae***
other, specify …

2. Complete name

(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 …

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:

(b) to which of the following organisms:

humans (**X**)
animals (.)
plants (.)
other ..

(b) are the donated sequences involved in any way to the pathogenic or harmful properties of the organism
Yes (.) No (**X**) 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
Human immunodeficiency virus: Risk 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 …

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

(d) 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
…

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
The recombinant virus may be detected using a "nested" PCR protocol developed by Huntingdon Life Sciences, UK for use in a GLP bio-distribution study in mice (Study MRC/013). This PCR method was used to monitor a range of mouse tissues for vaccine DNA sequences following repeated dosing with the MVA vaccine, based on two sets of primers specific for the HIVA open reading frame.

(b) Techniques used to identify the GMO
The identity of the MVA.HIVA construct may be checked by a series of eight PCR reactions on the insert

F. Information relating to the release

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

Phase 1 clinical trial

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 (X)

If yes, specify …

3. Information concerning the release and the surrounding area

(a) Geographical location (administrative region and where appropriate grid reference):
Municipal Health Service of Amsterdam, The Netherlands

(b) Size of the site (m^2): ***NA***
(i) actual release site (m^2): m^2
(ii) wider release site (m^2): m^2

(c) Proximity to internationally recognized biotopes or protected areas (including drinking water reservoirs), which could be affected:
None

(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:
Depending on the number of study participants (approximately 15 participants): 3 vaccines will be administered per participant of either 5 X 10^6; 5 X 10^7; 2,5 X 10^8 PFU MVA HIVA or placebo.

(b) Duration of the operation:
Study period per participant is 18 months. Expected enrollment for this phase 1 trial is approximately 6 months.

(c) Methods and procedures to avoid and/or minimize the spread of the GMOs beyond the site of the release
Protocols are available to: store, transport and administer the vaccine. Additionally protocols to adequately destruct all materials that have been in contact with the GMO are available. All these protocols contain the appropriate measures to avoid spread of the GMO in the environment.

5. Short description of average environmental conditions (weather, temperature, etc.)
In the Netherlands there is an average sea-climate.

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.

MVA is incapable of replication in humans and thus there should be no virus shedding from the vaccinated individuals.

The genetically modified viral vaccine is not able to survive, disseminate in and/or displace other organisms and is not pathogenic to animals or plants

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) ***NA***
   (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 …

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

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 (***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
   None

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) …
   (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:
None

(b) from other organisms to the GMO:
None

(c) likely consequences of gene transfer:
None

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.):
…

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

H. Information relating to monitoring

1. Methods for monitoring the GMOs

The recombinant virus may be detected using a "nested" PCR protocol developed by Huntingdon Life Sciences, UK for use in a GLP bio-distribution study in mice (Study MRC/013). This PCR method was used to monitor a range of mouse tissues for vaccine DNA sequences following repeated dosing with the MVA vaccine, based on two sets of primers specific for the HIVA open reading frame. The identity of the MVA.HIVA construct may be checked by a series of eight PCR reactions on the insert

2. Methods for monitoring ecosystem effects

MVA is incapable of replication in humans and thus there should be no virus shedding from the vaccinated individuals. The genetically modified viral vaccine is not able to survive, disseminate in and/or displace other organisms and is not pathogenic to animals or plants.

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

MVA is incapable of replication in humans and thus there should be no virus shedding from the vaccinated individuals. The genetically modified viral vaccine is not able to survive, disseminate in and/or displace other organisms and is not pathogenic to animals or plants.

4. Size of the monitoring area (m^2)
Not applicable.

5. Duration of the monitoring
Not applicable.

6. Frequency of the monitoring
Not applicable.

I. Information on post-release and waste treatment

1. Post-release treatment of the site
Surfaces that have been used during vaccination will be cleaned using 0.1% chloride-solution. All materials used during vaccination will be put in special containers and destructed according to procedures for hospital waste.

2. Post-release treatment of the GMOs
Used vaccine bottles will be transported back to the laboratory of the Municipal Health Service (where the vaccines are stored) using closed, unbreakable leakage-free containers. At the end of the study, all empty vaccine bottles will be destructed according to procedures for hospital waste. Unused vaccine will be returned to the sponsor, IAVI, according to regulations meant for the transport of GGO's.

3. (a) Type and amount of waste generated
Needles, syringes, cottonballs, dry adhesives, gloves, disposable aprons.

3. (b) Treatment of waste
Destruction according to procedures for hospital waste

J. Information on emergency response plans

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

Blood and vaccine that has been spilled during any of the vaccination procedures will be cleaned using absorbent material and 80% alcohol. All materials used during the cleaning procedures will be destructed according to procedures meant for the destruction of hospital waste.

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

Blood and vaccine that has been spilled during any of the vaccination procedures will be cleaned using absorbent material and 80% alcohol. All materials used during the cleaning procedures will be destructed according to procedures meant for the destruction of hospital waste.

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
Not applicable