Memorandum

File Ref: DMNO/01/NOQ07001

To: Decision-making Committee

Copy to Libby Harrison, Geoff Ridley, Asela Atapattu

From: Andrea McNeill and Kirsty Allen

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Subject: Covering memo for the draft decision NOQ07001

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1 Overview

1.1 This memo was written by the Agency to accompany the draft decision for NOQ07001. As this is the first Qualifying Organism decision, the memo briefly:

- describes the background to this application;
- provides more information about the section of the ACVM Act 1997 which describes what a veterinary medicine is;
- describes the possible ACVM controls that could be imposed;
- describes the current Authority policies on Qualifying Organisms; and
- outlines the comments from MAF BNZ, DOC and ACVM.

2 Background to NOQ07001

2.1 MAF Biosecurity New Zealand (MAF BNZ) have applied to import for release Flu Avert® I.N. vaccine – a vaccine against equine influenza (EI) (an influenza A virus). Flu Avert® I.N. vaccine contains a cold adapted, attenuated, strain of equine influenza.

2.2 The EI virus in the Flu Avert® I.N. vaccine was produced by serial passage at progressively lower temperatures. The project team considers that this protocol does not fall under the definition of genetic modification under the HSNO Act (the Act).

2.3 MAF BNZ has stated that Flu Avert® I.N. vaccine may be used to help contain or prevent an outbreak of EI only once the disease is identified as being present in New Zealand and that pre-emptive vaccination using this vaccine is not currently considered an option.

2.4 MAF BNZ were advised that as the status of all influenza A strains in New Zealand has not been formally determined by the Authority (via a section 26 application), the Agency considers equine influenza to be a new organism under the Act and therefore a release application is required for this vaccine.

2.5 The project team note that section 38L of the Act states that the Authority can review any controls imposed on an approval to release a Qualifying Organism. Therefore, the project team proposes that a control be imposed (**proposed control 1**) that allows the review of any control if the status of EI in Australia or New Zealand changes.

2.6 The project team notes that only medicines that are considered low risk to the environment or to public health can fulfil the Qualifying Organism criteria.

3 Assessment against the criteria of a Qualifying Organism

3.1 Section 38I of the Act can be found in **Appendix 1**.

3.2 To assess the Flu Avert® I.N. vaccine against the criteria of a Qualifying Organism or Qualifying Medicine, the project team firstly considered whether Flu Avert® I.N. vaccine meets the criteria as a veterinary medicine under the Agricultural Compounds and Veterinary Medicines Act (ACVM) Act 1997 (**section 3.8–3.10** of this memo). The project team then looked at the possible ACVM conditions that could be imposed when the vaccine is registered by the ACVM Group and which controls may mitigate the effects of the organism on public health and the environment **(sections 3.11-3.18** of this memo**).**

3.3 In accordance with section 38I(3)(b) of the Act and clauses 10(e) and (f) of the Methodology, the project team firstly considered whether a self-sustaining population would be undesirable, and then considered the ability of the organism to form an self-sustaining population and the pathways by which a self-sustaining population could form. During the consideration of these pathways, the project team proposed controls to prevent the formation of a self-sustaining population.

3.4 The project team notes that the current policy on Qualifying Organisms in "*Policy documents relating to New Organisms*" (ER-PO-NO-01-4 05/06 May 2006) (**Appendix 2**) states that to provide assurance that environmental or public health risks are adequately managed throughout the lifecycle of the organism (including when any change in use of the veterinary medicine is contemplated), the Authority will impose a control relating to the methods of administering the qualifying medicine or qualifying veterinary medicine. Such a control will have a review provision included pursuant to section 38L(1)(b) of the Act.

3.5 The project team also notes that this policy states that the Authority will set controls relating to the storage and disposal of the qualifying organism unless information is provided as to why controls are not necessary.

3.6 After taking the proposed controls into account and in accordance with s38I(3) and the Matters in Part II of the Act, the project team identified and assessed any significant adverse effects on public health and safety, the environment, Maori and their relationship with the environment, society and community, the market economy and any significant adverse effects the dose and route of administration of the vaccine could have on the health of the public and any valued species or if the vaccine virus

could form an undesirable self-sustaining population and have significant adverse effects that could have on the health and safety of the public, valued species, natural habitats, or the environment.

ACVM criteria for a veterinary medicine

3.7 The project team notes any effects of the vaccine on the animal treated with that vaccine are not to be taken into account (section 38I (4)(b) of the Act). These effects will be assessed during the ACVM registration process.

3.8 The project team notes that section 2 of the ACVM Act 1997 states that "*Veterinary Medicine means any substance, mixture of substances, or biological compound used or intended for use in the direct management of an animal*" and biological compound "*means any agricultural compound that is (a) A preparation of animal origin; or (b) A bacterial or* ***viral vaccine, whether living or not****; or (c) A virus, mycoplasma, or other micro-organism, whether living or not; or (d) A product of a virus, mycoplasma, or other micro-organism, or any substance manufactured for the purpose of having the same action as a product of a virus, mycoplasma, or other micro-organism*".

3.9 Therefore, the project team considers that Flu Avert® I.N. vaccine falls under the criteria as a veterinary medicine as it is a biological compound (a viral vaccine) that is intended for use in the direct management of an animal.

Possible ACVM controls

3.10 The project team notes that for the registration of any agricultural compound or veterinary medicine, conditions that list the requirements for the importation, sale and use are imposed by the ACVM Group. These conditions can be chosen from a standard list of conditions and in addition, product specific conditions can be imposed. ACVM consideration will take place after ERMA New Zealand consideration and therefore the exact conditions that will be imposed by the ACVM are not known. The project team has considered which ACVM controls may be expected to be imposed on the vaccine.

3.11 The project team noted that the applicant has listed ACVM controls that have previously been applied to vaccines containing live organisms such as (a) Equine arteritis virus and (b) Canine distemper virus, canine adenovirus type 2, canine parainfluenza virus and canine parvovirus. The project team also took into account the ACVM conditions for the inactivated EI vaccine Equilis IPA Influenza vaccine.

3.12 The project team noted that the ACVM conditions common to these three approvals are Condition 2 (manufacture of the product in accordance to Good Manufacturing Practice), Condition 11 (compliance of labelling with ACVM requirements) and Condition 37 (Notification of adverse events or new studies/data that contradict previous information supplied to ACVM).

3.13 The project team notes that the exact conditions imposed relating to the importation, use or sale of the vaccines vary depending upon the vaccine involved. For example, Condition 31 states that the product is to be used as specified in the label content, Condition 14 states that the product is to be administered to an animal only in the presence of or under control of a veterinarian or by a veterinarian, and Condition 15

states that the product is to be administered under and in accordance with the authority or prescription of a veterinarian.

3.14 The project team also notes that product specific conditions were imposed for the Equilis IPA Influenza vaccine. The project team notes that the additional conditions imposed in "Product Specific Approval" documentation can include requirements for the distribution and use of the vaccine; for an inventory to be maintained and for the identification of vaccinated animals and maintenance of a register.

3.15 The project team considers that controls that ensure the manufacture of vaccine according to international standards, which require the veterinary medicine to be used as per label, or which limit the use of the vaccine to veterinarians could mitigate specific adverse effects on public health or the environment.

3.16 Although the project team expects that similar types of ACVM controls will be imposed for the Flu Avert® I.N. vaccine, as the ACVM registration process will not be completed until after this application is considered, we cannot guarantee which ACVM controls will be imposed.

3.17 To receive input from the ACVM Group, the draft HSNO Act controls were sent to ACVM for comment. The project team considers that if, during the ACVM registration process, any of the imposed HSNO Act controls conflict with the ACVM conditions, that an appropriate course of action would include a review (under section 38L of the Act) of that control (proposed control 1 in the draft decision).

4 Assessment of adverse effects

4.1 The project team notes that in accordance with clause 24 of the Methodology and section 38I(3), it must be considered whether the dose and route of administration of the medicine or veterinary medicine would have **significant adverse effects** on the health of the public or any valued species, and whether the qualifying organism could form an **undesirable self-sustaining population and** would have **significant adverse effects** on the health and safety of the public; or any valued species; or natural habitats; or the environment. In addition, as per sections 5, 6 and 8 of the Act and parts of clauses 9 and 10 of the Methodology, the project team assessed the potentially significant adverse effects in the relationship of Maori to the environment, society and community and the market economy.

4.2 The project team notes that in the "Policy documents relating to New Organisms" (**Appendix 2**), a number of policy guidelines are described to assist with the implementation of the rapid assessment provisions for Qualifying Organisms. The term "highly improbable" is defined as "*Almost certainly not occurring but cannot be totally ruled out*". A "significant adverse effect" on the matters set out in section 38I(3)(a)(ii) and (b)(ii-iv) means any effect on valued species that is *"Measurable long term damage to local plant and animal communities, ... medium term individual ecosystem damage"* and a "significant adverse effect" on public health set out in section 38I(3)(a)(i) and (b)(i) is interpreted as meaning *"Minor irreversible adverse health effects to individuals and/or reversible medium term adverse effects to a larger (but surrounding) community (requiring hospitalisation)."*

5 Decision path

5.1 The current decision pathway for Qualifying Organism is in **Appendix 3**. The Committee should note that, as this decision path has not previously been used, some changes to the pathway or associated notes may be required to clarify the consideration process. This can be discussed during the Consideration.

6 Comments from MAF, DOC and ACVM

6.1 The full written comments from MAF BNZ and DOC can be found in **Appendix 4**. These submissions can be discussed where appropriate during the Consideration. The main points are outlined below.

DOC submission

6.2 The project team considers the major points of the DOC submission are:

- DOC would like a control restricting the use of this vaccine a until a confirmed EI disease outbreak.

  Response: This point will be discussed further at the Consideration.

- DOC would like a control imposed requiring medicine to be used to limit coughing by vaccinated horses.

  Response: The project team notes that only a very small proportion of vaccinated horses cough and a control requiring the dosing of all vaccinated horses is impracticable. The project team consider that the proposed control requiring the isolation of vaccinated horses from unvaccinated horse (proposed control 5.5) will be sufficient to prevent spread by coughing.

- DOC would like a control imposed concerning the disposal of carcasses/meat of recently vaccinated horses.

  Response: The project team has proposed control 5.8 which states that for a period of 14 days post-vaccination, animal products (ie raw meat) from a vaccinated horse should be treated as biohazard waste and disposed of accordingly.

- DOC noted that the AUSVETPLAN stated that domestic horses should be confined at least 50 metres away from feral horses and did not think that Kaimanawa horses could be kept separate from vaccinated domestic horses.

  Response: The project team notes that the AUSVETPLAN refers to a proposed strategy when an EI outbreak occurs. The project team notes that the vaccine contains an attenuated virus and not the virulent wild type virus the strategy above is targeted towards. The project team considers that, as only a very small percentage of vaccinated horses have been shown to cough and as the vaccine virus is attenuated, the proposed control requiring the isolation of vaccinated horses from unvaccinated horse (proposed control 5.5) will be sufficient to prevent spread by coughing.

MAF BNZ submission (the applicant)

6.3 Comments from the applicant will be forwarded to the Committee when they arrive.

MAF BNZ submission (compliance)

6.4 The main points of the MAF BNZ submission are:

- MAF BNZ states that the risk analysis previous performed by MAF BNZ for this vaccine is included on page 10 of the application;
- In addition, MAF BNZ identified that live virus may be excreted for a short time from the recipient and that the risk analysis concluded that any in-contact horse that might be infected from an excreting recipient of the vaccine would be "vaccinated" with no adverse effects likely; and
- MAF BNZ states for registration under the ACVM Act, a risk assessment will be required where ACVM look at whether the manufacturing processes in place are effective, and what testing the company routinely does for adventitious agents.

Comments on proposed controls (please note that the numbers of the controls referred to in the submission refer to an earlier set of controls. The correct control number is referred to below):

- MAF BNZ considered that it may be impractical to vaccinate every horse on a property within timeframes of a co-ordinated response and that isolation of non-vaccinated horses from vaccinated horses is a preferred alternative. MAF BNZ considered that if it is not possible to isolate vaccinated horses from non-vaccinated horses, depending on the buffer zones required, then vaccination of all horses would be required.

  Response: The project team have outlined in paragraph 7.1 why the vaccination of all horses on a property is not feasible. The project team considered a proposed control requiring the isolation of vaccinated horses from unvaccinated horses (proposed control 5.5) should be sufficient.

- MAF BNZ considered that in proposed control 5.6, an explicit connection between "correct handling procedures" and veterinary training as proposed in control 4 was required.

  Response: The project team will ensure that the finalised controls are clearly written to avoid any ambiguity.

- MAF BNZ considered that it may be difficult to enforce hand-washing after contact with horses for 10 days post-vaccination (proposed control 5.4 and 5.6).

  Response: If this application has been approved, the project team will discuss with MAF BNZ the controls imposed and ERMA New Zealand's expectations about how these controls will be met (in a practicable manner) and audited.

- MAF BNZ considered that it may be necessary to define which "equipment" is included under this control, otherwise bridles, bits, halters and other tack could be included and suggest changing "ie Virkon" to "eg Virkon" (proposed control 5.4).

  Response: The project team will ensure that the finalised controls are clearly written to avoid any ambiguity.

- MAF BNZ queried that as horses are presumably likely to sneeze during and after receiving intranasal vaccine - is disinfection of stalls or holding areas after 10 days vaccination treatment required?

  Response: The project team notes that proposed control 5.4 requires that equipment (including the vaccine vial and applicator) or other material (including clothing) that comes into contact with the vaccine should be thoroughly cleaned by an appropriate method or treated as biohazard waste and disposed of accordingly. This control would also apply to surfaces the horse has "sneezed" the vaccine onto. The project team note that influenza A viruses can survive for only limited time on hard non-porous surfaces (24-48 hours), for cloth, paper and tissues (from <8 to 12 hours) (Bean et al, 1982) and in the sunlight and believe that the 14 day post-vaccination period will ensure that no viable viruses will remain.

ACVM submission

6.5 The project team met with Neil Kennington from ACVM to discuss the controls in the draft decision. During this meeting the following points were noted:

- MAF BNZ have yet to apply to ACVM for registration of Flu Avert® I.N. vaccine.
- If there is not sufficient information on the attenuation of the vaccine or if there is a possibility of reversion to virulence of the vaccine virus, ACVM may restrict the use of this vaccine for emergencies only (ie when EI is already in New Zealand).
- ACVM will look at the effect this vaccine may have on trade, interference with surveillance programmes for EI and entry of this vaccine into the food chain.
- ACVM are concerned that a proposed control referring to the Material Safety and Data Sheet and placing strict controls on the requirement for safety equipment (ie safety glasses) may give the impression that the vaccine could have adverse effects on humans (ie is zoonotic). The project team considered this point and reworded the proposed controls.
- ACVM will impose a quarantine period either based on the Import Health Standards for importing horses quarantine period or based on a plan supplied by MAF BNZ to ACVM.
- ACVM would want a handout to be supplied with the vaccine outlining HSNO and ACVM Act controls.
- ACVM consults with MOH when registration of live vaccines is applied for.

6.6 Comments from ACVM on the draft decision will be forwarded to the Committee when they arrive.

7 Additional points to note

7.1 The project team had a meeting with the applicant to discuss the proposed controls. At this meeting, the applicant noted that a control that had been suggested in their application (that all horses on a property be vaccinated) is now not feasible as (a) MAF BNZ would not want to vaccinate a horse that is infected with EI (this will also remove the opportunity for reassortment occurring between the vaccine virus and wild

type virus) or (b) vaccinate horses that have seroconverted (ie already have resistance to EI after being naturally exposed). The project team considers that these reasons are valid and therefore has not proposed this control.

7.2 The project team also noted that the applicant wanted references to "veterinary assistants" removed and therefore only veterinarians will administer this vaccine.

7.3 The project team will also discuss with the Committee during the Consideration whether a control is required restricting the use of this vaccine to when the presence of EI has been confirmed in New Zealand.

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Appendix 1: Section 38I to 38L of the Act

Release of qualifying organisms

38I. Assessment of applications for release of qualifying organisms–

(1) If the Authority receives an application under section 34 that relates to a qualifying organism, the Authority may –

(a) make a rapid assessment of the adverse effects of importing for release or releasing from containment the qualifying organism; and

(b) approve the importation for release or the release from containment of the qualifying organism with or without controls.

(2) If the Authority does not approve an application under this section, the Authority must assess and determine the application under section 38.

(3) The Authority or the responsible chief executive, as the case may be, may determine that a qualifying organism is or is contained in a qualifying medicine or a qualifying veterinary medicine only if satisfied that, taking into account all the controls that will be imposed (if any), it is highly improbable that-

(a) the dose and routes of administration of the medicine or veterinary medicine would have significant adverse effects on-

(i) the health of the public; or

(ii) any valued species; and

(b) the qualifying organism could form an undesirable self-sustaining population and would have significant adverse effects on-

(i) the health and safety of the public; or

(ii) any valued species; or

(iii) natural habitats; or

(iv) the environment.

(4) In determining under subsection (3) whether a qualifying organism is or is contained in a qualifying medicine or a qualifying veterinary medicine, the following effects (if any) are not to be taken into account:

(a) any effect of the medicine or qualifying organism on the person who is being treated with the medicine:

(b) any effect of the veterinary medicine or qualifying organism on the animal that is being treated with the veterinary medicine.

(5) An approval granted under this section is not an approval-

(a) to use a qualifying medicine until the medicine has been lawfully supplied for use under the Medicines Act 1981; or

(b) to use a qualifying veterinary medicine until the veterinary medicine has been approved for use under the Agricultural Compounds and Veterinary Medicines Act 1997.

38J. Procedure for assessing and approving application by responsible chief executive- If the Authority has delegated to the responsible chief executive its power to assess and approve an application under section 38 for the release of a qualifying organism, the responsible chief executive must-

(a) be paid the fee set by the Authority for the assessment and approval of the application; and

(b) determine whether the medicine is a qualifying medicine or the veterinary medicine is a qualifying veterinary medicine, as the case may be; and

(c) if the responsible chief executive is satisfied that the medicine is a qualifying medicine or the veterinary medicine is a qualifying veterinary medicine, the responsible chief executive may, with or without controls, approve the release of the qualifying organism.

38K. Controls- (1) The type of controls that may be imposed on the importation for release or release from containment of a qualifying organism include-

(a) controls for the distribution of the qualifying medicine or qualifying veterinary medicines:

(b) controls providing for the methods of administering the qualifying medicine or qualifying veterinary medicine:

(c) controls concerning the persons who may administer the qualifying medicine or qualifying veterinary medicine:

(d) controls concerning the persons to whom the qualifying medicine may be administered:

(e) controls concerning the animals to which the qualifying veterinary medicine may be administered.

(2) Subsection (1) does not limit the type of controls that may be imposed on the importation for release or release from containment of a qualifying organism.

38L. Review of controls for qualifying organisms- (1) The Authority may, on its own initiative or on the application of the holder of an approval under section 38I or of any person specified in section 97 or section 97A, review any controls that it has imposed on the approval, but only if-

(a) the review is to amend a controls so that it better meets the objective of the control; or

(b) the controls included a review requirement specifying-

(i) the circumstances in which the control would be reviewed; and

(ii) the potential consequences of the review.

(2) The Authority-

(a) may carry out the review without publicly notifying the review in accordance with section 53; but

(b) if it does so, must-

(i) consult, and consider the views of, any government agency (as defined in section 49A) that the Authority considers is likely to have an interest in the review; and

(ii) publicly notify the results of the review.

(3) This section does not limit section 67A.

Appendix 2: "Qualifying Organisms" Policy documents relating to New Organisms" ER-PO-NO-01-4 05/06 May 2006 pages 29-32

Considering Applications for the release of Qualifying Organisms by rapid assessment

Introduction

1. The Act provides for a new category of approval allowing for the rapid assessment of a qualifying organism that is to be released as a medicine or veterinary medicine. The Act also enables rapid assessments to be delegated to the Chief Executives of ERMA New Zealand, the Ministry of Health (in the case of a medicine) and the Ministry of Agriculture and Forestry (in the case of a veterinary medicine).

2. The Authority has developed a number of policy guidelines to assist with the implementation of the rapid assessment provisions. These relate to specifying when an organism meets the criteria for rapid assessment and include:
- Guidance on how the terms "highly improbable" and "significant" should be interpreted
- Guidance on what controls need to be considered when assessing the rapid assessment criteria
- Setting HSNO controls that should be expected to be applied to all rapid assessment approvals

Interpreting "highly improbable" and "significant"

3. The Act uses these terms as threshold descriptors for deciding on whether or not an organism can be rapidly assessed and released as a qualifying organism. The two descriptors are best interpreted using a risk assessment framework. The HSNO Methodology Order sets out an approach for dealing with these terms by utilizing the concepts of likelihood and magnitude. So in a risk assessment framework the term "highly improbable" is looking at the likelihood side of the risk equation and "significant" at the magnitude side. Combined together the two concepts provide the commonly accepted definition of risk.

4. The Authority has developed qualitative descriptors for different levels of likelihood and magnitude of consequence.

5. In terms of likelihood the Authority recognises seven categories ranging from "highly improbable" through to "extremely likely". The term "highly improbable" is defined as: *"Almost certainly not occurring but cannot be totally ruled out."*

6. This term as used by the Authority represents the most remote or unlikely scenario in the range of descriptive criteria used. The situation where an event may be described as "not occurring ever" may be theoretically possible but is considered to be unrealistic and inappropriate in the real life situations to which the Authority must make decisions.

7. An example of a situation where the dose and route of administration of a qualifying organism is "highly improbable" to cause an adverse effect is the intramuscular injection of a vaccine that is imported and distributed in sealed single dose ampoules.

8. An example of a situation where it may not be "highly improbable" that the dose and route of administration of a qualifying organism will cause an adverse effect is the oral dosing of animals using a veterinary medicine containing an organism that will survive passage through and be excreted from the animal into the environment. In this situation because the "highly improbable" test could not be met, further assessment of the effects of the organism would be required. Therefore the medicine would not be suitable for rapid assessment under the provisions of section 38I.

9. In terms of magnitude the Authority uses qualitative descriptors ranging from minimal through to massive. Using these descriptors a "significant adverse effect" on the matters set out in section 38I(3)(a)(ii) and (b)(ii-iv) means any effect on valued species that is:
"Measurable long term damage to local plant and animal communities, ... medium term individual ecosystem damage."

10. Effects that are more severe then these obviously are also regarded as "significant".

11. Key aspects for deciding on whether the qualifying organism will cause significant adverse effects to valued species should consider both short and long term issues.

12. In regard to the consideration of long term issues aspects that should be considered are firstly whether the organism can establish a self-sustaining population and secondly, if it does the extent to which this population affects the ecosystem it establishes in. In order to enable these determinations to be made the applicant will be required to provide sufficient relevant information on the biological characteristics of the organisms with the application.

13. For short term issues the key aspects to be considered are the biological hazards (such as pathogenicity, virulence, or predator characteristics) and the pathways by which local ecosystems may be exposed. Where the organism possesses biological characteristics that may adversely affect local ecosystems (for example pathogenic infection of fish) then the likelihood (see above) that the proposed dose and route of administration will lead to fish being exposed to the qualifying organism needs to be considered.

14. Section 38I(4)(b) also indicates that while adverse effects to target individuals or organisms are excluded, effects on non-target animals would be included in this assessment.

15. A "significant adverse effect" on public health set out in section 38I(3)(a)(i) and (b)(i) is interpreted as meaning:
"Minor irreversible adverse health effects to individuals and/or reversible medium term adverse effects to a larger (but surrounding) community (requiring hospitalisation)."

16. Effects that are more severe then these obviously are also regarded as "significant".

17. Key aspects for determining these effects will be obtained from information on the toxicity and pathogenicity of the organism to humans. This information will cover aspects such as biological activity, stability and bioavailability, dose range for toxicity, host range, target tissues and organs, virulence, infectivity, and the nature of any side effects in humans.

18. An example of a medicine that may be considered not to cause significant adverse effects on public health is the cholera vaccine Orochol®. This vaccine contains the viable bacterial strain, *Vibrio cholerae* CVD 103-HgR which is genetically modified so that it can't produce the cholera toxin. This organism may be considered low-risk because it cannot cause disease and is not harmful to people who may be accidentally exposed to the vaccine based on data from clinical trials. In addition, the likelihood of the GM bacteria regaining the ability to produce the cholera toxin via gene transfer from toxin-producing bacteria present in the environment is improbable. If this particular hazard were to be realized, it would not pose any risks additional to those posed by cholera-toxin producing bacteria already present in the environment.

19. An example of a medicine that may be considered to potentially cause significant adverse effects on public health is the smallpox vaccine. This vaccine is not genetically modified and contains the live vaccinia virus which is infectious, able to spread within the body of the vaccinated person and to other non-vaccinated people (inadvertent inoculation) within the community and may cause severe complications in some people to whom the virus has spread e.g. people with weakened immune systems (i.e. HIV positive, transplant recipient or cancer patients), skin conditions (e.g. eczema or atopic dermatitis), or heart conditions. It is known that these effects can occur as potentially life threatening reactions to the small pox vaccine have been observed in 14-52 out of every 1 million people vaccinated for the first time in the past.

Relevant Controls

20. Section 38I(3) of the Act states:
"The Authority....may determine that a qualifying organism is or is contained in a qualifying medicine or a qualifying veterinary medicine only if satisfied that, taking into account all the controls that will be imposed (if any)..."

21. The Authority recognises that the key factors which influence the environmental and public health risks posed by medicines are the dose and routes of administration. For both human medicines and veterinary medicines, these factors can be controlled by the requirements of the principal legislation regulating these products. In the case of human medicines the principal legislation is the Medicines Act 1981, and in the case of veterinary medicines the Agricultural Compounds and Veterinary Medicines Act, 1997.

22. Human or veterinary medicines cannot be legally used without an appropriate regulatory approval. Such approvals will have a range of mandatory controls imposed which regulate how the medicine can be used. Therefore it is appropriate to consider the impact of these use related controls when considering the risk of the organism to the environment and public health. Hence the Authority will consider the range of controls that are likely to be imposed on medicines either under the Medicines Act in the case of a human medicine or the ACVM Act in the case of a veterinary medicine when making decisions under sections 38I(3)(a) and (b).

HSNO Act Controls

23. As discussed above the key factor influencing risks to the environment and public health of an organism that is, or is contained in a medicine, is how the medicine is to be used, or in other words, the route of administration and dose. These factors will initially be managed by controls set under the principal legislation (Medicines or ACVM Acts) but unless a HSNO Act control is placed on the approval, there will be no mechanism for reassessing or reviewing the environmental or public health risks of the organism if the use controls of the qualifying organism are changed under these other pieces of legislation. This is because under the HSNO Act, the organism becomes an unregulated organism if no controls are placed on the approval i.e. it is an uncontrolled release.

24. As neither the Medicines Act nor the ACVM Act consider environmental or public health effects of medicines in the process of approval, the Authority needs to be assured that such risks are adequately managed through-out the lifecycle of the organism including when any change in use of the medicine is contemplated.

25. To provide this assurance the Authority will as a matter of course impose a control relating to the methods of administering the qualifying medicine or qualifying veterinary medicine. Such a control will have a review provision included pursuant to section 38L(1)(b) of the HSNO Act.

26. As a general matter of course the Authority will set controls relating to the storage and disposal of the qualifying organism. These are two important lifecycle components where wider effects to the environment and public health may not be adequately covered by a normal medicines or veterinary medicines approval. As the setting of such controls is discretionary in section 38K(2) the default position is that they will be set unless information is provided, primarily by the applicant but also from any other source, as to why they are not necessary.

Appendix 3: Current Decision pathway

Figure 8

Decision path for applications to import for release or release from containment a medicine or veterinary medicine that contains a qualifying organism

Context

This decision path describes the decision-making process for applications to **import for release or release from containment a medicine or veterinary medicine that contains a qualifying organism**. These applications are made under section 34 of the HSNO Act, and determined under section 38I of the Act. If the application is 'not approved' then the Authority **must** proceed to consider the application under Section 38 of the Act.

Introduction

The purpose of the decision path is to provide the Authority with guidance so that **all relevant matters** in the HSNO Act and the Methodology have been addressed. It does not attempt to direct the weighting that the Authority may decide to make on individual aspects of an application.

In this document 'section' refers to sections of the HSNO Act, and 'clause' refers to clauses of the ERMA New Zealand Methodology.

The decision path has two parts –

- **Flowchart** (a logic diagram showing the process prescribed in the Methodology and the HSNO Act to be followed in making a decision), and
- **Explanatory notes** (discussion of each step of the process).

Of necessity the words in the boxes in the flowchart are brief, and key words are used to summarise the activity required. The explanatory notes provide a comprehensive description of each of the numbered items in the flowchart, and describe the processes that should be followed to achieve the described outcome.

For proper interpretation of the decision path it is important to work through the flowchart in conjunction with the explanatory notes.

Figure 8 FLOWCHART

Decision path for applications to import for release or release from containment a medicine or veterinary medicine that contains a qualifying organism (application made under section 34 of the Act and determined under section 38I of the Act)

For proper interpretation of the decision path it is important to work through the flowchart in conjunction with the explanatory notes

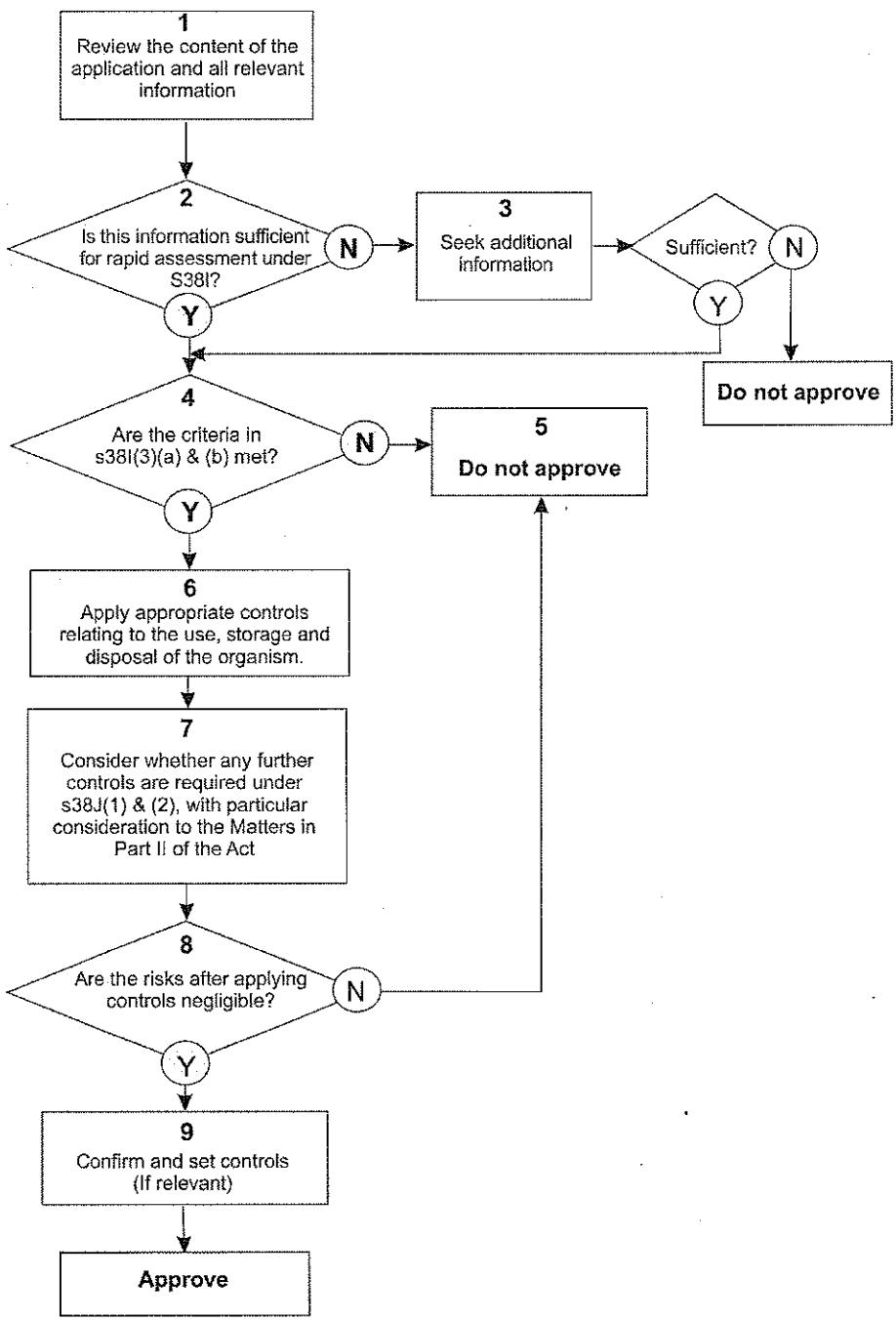

Figure 8 EXPLANATORY NOTES

If the application is 'not approved' then the Authority **must** proceed to consider the application under Section 38 of the Act.

Items 1, 2 & 3: Information that should be reviewed includes that in the application and from experts (where relevant). Review should occur in terms of section 34(2) of the Act and clauses 8, 20, 22 and 23 of the Methodology. Additional information may need to be sought under s58 of the Act.

If the applicant is not able to provide sufficient information for consideration then the application is not approved. In these circumstances the Authority may choose to decline the application, or the application may lapse.

Item 4: Determine whether the application relates to a qualifying organism.

Step 1: Consider whether the medicine the organism is to be released in meets the definition of a medicine or new medicine, or a veterinary medicine, under the Medicines Act 1981 or the Agricultural and Veterinary Medicines Act (ACVM) 1997.

Step 2: Identify the controls that will be set under the Medicines Act for a medicine, or the ACVM Act for a veterinary medicine that will mitigate the effects of the organisms on public health and the environment.

The starting point for these controls is the list of possible controls set out in section 38K(1).

Step 3: Taking into account the controls identified in Step 2 determine whether the medicine or veterinary medicine meets the requirements of section 38I(3)(a).

Step 4: Taking into account the controls identified in Step 2 determine whether the medicine or veterinary medicine meets the requirements of section 38I(3)(b).

Item 5: If the application fails the rapid assessment criteria the Authority may decide to

"not approve" the application.

Under section 38I(2) of the Act if the application is 'not approved', the Authority is required to consider it under section 38. However, should the application fail the rapid assessment criteria the applicant has the discretion to either provide the necessary further information and proceed to full assessment, or to choose to withdraw it.

Item 6: The Authority will as a general matter of course impose a control relating the approval to the methods of administering the qualifying medicine or qualifying veterinary medicine. This control will contain a review provision (section 38L (1)(b). The control (and approval) will be reviewed if there is any change in the methods administration.

In addition controls relating to the storage and disposal of the organism will usually be imposed. These are two important lifecycle components where wider effects to the environment and public health may not be adequately covered by a normal medicines or veterinary medicines approval. In each case these controls will be reviewed for relevance.

Item 7: The Authority will then consider whether there are other risks that should be controlled to give effect to the purpose of the Act with particular reference to Part II of the Act including, but not limited to all the matters in section 6.

In addition to controls listed in section 38K (1) section 38K(2) provides the power for the Authority to consider any additional controls that may be imposed.

In doing so, the Authority must consider the likely effectiveness of the identified controls, and extent and impact.

In addressing the likely effectiveness, the Authority must be satisfied that the controls set under HSNO Act take into account the controls also set any other regulatory regimes (e.g. the Medicines Act or the ACVM Act) in order to ensure that the adverse effects of the qualifying organism are mitigated to the

extent required.

The range of risks to be identified and assessed should be that covered by sections 4, 5 and 6 of the Act, and clauses 9, and 10 of the Methodology. There are three steps within this part of the process:

Step 1: Assessment of the likelihood of an adverse effect occurring and the magnitude of that effect if it should occur.

Step 2: Consideration of the extent to which the risk will be mitigated by the ability to eradicate the organism if a significant adverse effect eventuated.

Step 3: Consideration of how risk averse or cautious the Authority should be in giving weight to the resulting or remaining risk, in terms of clause 33 of the Methodology.

Item 8: If the residual risks are significant, e.g., if there are still cultural objections after applying controls, rapid assessment is not appropriate. The result is thus to "not approve", but with the option of the application being reconsidered after the provision of further information as a full assessment.

Item 9: Set controls, or release without HSNO controls. Controls have been considered at the earlier stages of the process (items 4, 6 & 7).

Reference should be made to the list of controls set out in section 38K (1) in the process of confirming and setting the controls.

If controls are changed at this point, the previous steps need to be repeated.

Appendix 4: Written comments from DOC and MAF BNZ

DOC submission received 5 December 2007

Comments on the Application for approval to release a Qualifying Organism by Rapid Assessment.

Application code:	**NOQ07001**
Applicant:	**Ministry of Agriculture and Forestry**
Purpose:	**To release FluAvert® I.N., an intranasal vaccine to be used to prevent or combat an outbreak or in vaccination programmes against equine influenza.**

Thank you for the opportunity to review this application. The Department has the following comments:

General comments:

Risk greater for live vaccines

The Department notes that live vaccines present a greater risk to the environment than killed vaccines. This is due to their ability to multiply and establish, and also, in the case of modified live vaccines (MLV), to revert back to more virulent strains. Therefore we consider it essential that a precautionary approach be taken to their approval and use.

Status of Equine Influenza (EI) in New Zealand

We note that use of a live vaccine that is a "New Organism" may result in confusion regarding the status of the organism and its "presence" in New Zealand. This can have significant consequences, including in the current case the loss of New Zealand's EI freedom status by the OIE. The Department therefore fully supports ERMA's imposition of strict controls on any approval that will mitigate this risk by limiting the 'qualifying organism's' use with suitable controls until such a time as there is evidence that the use of a MLV is necessary to manage a confirmed EI disease outbreak.

Conditions suggested by the applicant

We congratulate the applicant on proactively identifying conditions, which we consider go along way to mitigating the risks of the release of this MLV.

Specific comments

Survivability of the cold-adapted live virus.

We note that there is no direct evidence presented on the length of time the cold-adapted virus can survive in the environment, including contamination of hard surfaces or in cool moist areas such as soil and hay etc. The information provided relates to EI virus (which survives at higher temperatures 34°C) and therefore there is some possibility that the cold adapted-virus (which survives at 26°C) could survive for longer periods outside of the horse's nasal passage. It is therefore suggested that quarantine measures may require reviewing to ensure they are fully efficacious. For example a longer quarantine time of 14 days may be more suitable to ensure that viral material shed up to 10 days after immunization is not viable as a contaminant. This may also have implications for the size of the containment zone as cooler air temperatures/longer survival may mean that the virus is able to spread over greater distances.

Spread of aerosols

We note at section 3.5 that the applicant details that close contact is required for the transmission of human viruses to other individuals. The Department notes that this is not necessarily the case with EI (or the MLV) with the AUSVETPLAN citing cases of windborne spread of EI up to 35 metres and possibly further under favorable air and wind drift conditions, and a case of 8 kilometres reported anecdotally in South Africa[1].

We suggest that the use of medicines to limit coughing by immunised horses (noting that only minor coughing occurs in immunised horses) could be useful to further reduce the release of viral material and therefore the inadvertent spread to other horses.

Infection of species other than equid mammals

We note that the AUSVETPLAN details that EI virus may survive in fresh, chilled or frozen meat[2]. Therefore there is some possibility that other species apart from equid mammals may become infected as a result from the consumption of contaminated uncooked horsemeat. We suggest that this could have been a possible cause of the infection of the greyhound dogs in

[1] AUSVETPLAN Disease Strategy Equine Influenza Version 3.0, 2007,p18.
[2] Ibid, p26.

the USA[3] and as research has also shown that humans can be experimentally infected with EI, this also has potential ramifications for human health. Therefore consideration should be given to the imposition of a control limiting the disposal of carcasses/meat of recently vaccinated horses.

Impact on populations of equines such as the Kaimanawa horses, and Zebra in containment.

The Department notes that there is little evidence of the efficacy or impacts of this MLV on naive equine populations and in particular for Zebra and the wild Kaimanawa horses. Given the isolation of these groups either naturally or as a result of zoo containment, these populations may have a different level of tolerance to the effects of the MLV and monitoring of any vaccination of these groups will be required.

The AUSVETPLAN [4] details that domestic horses should be confined at least 50 metres away from feral horses. This is likely to be necessary for horses kept near the Hamilton Zoo, which is situated near the town boundary and were zebras are resident. Such an exclusion zone is likely to be problematic for the Kaimanawa horses that roam freely including near adjacent farmland where domestic horses may or may not be resident.

Conclusions

The Department notes that there is a level of risk associated with the approval of a modified live vaccine including that it can revert to a more virulent strain. However, in the present case, the release of this cold adapted virus is only proposed in response to a confirmed outbreak of Equine Influenza such that the release of the MLV will have no greater negative impacts than is likely to occur from the outbreak itself. We note that the release of the vaccine will have consequences for the EI freedom status of New Zealand and consider that further analysis and consensus would be needed before a preemptive use of the vaccine should be approved.

The Department does not oppose the approval of the release of this "qualifying organism' for emergency use only.

Comments provided on behalf of the Department of Conservation by:

Leanne Perry-Meyer

Biosecurity Technical Officer

Biosecurity Section

Research, Development and Improvement Division

Wellington.

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[3] Ibid, p9.

[4] Ibid, p37.

MAF BNZ submission received 10 December 2007

Submission Form to ERMA New Zealand for New Organism Applications

Application Code:	NOQ07001
Applicant Name:	Ministry of Agriculture and Forestry, Biosecurity New Zealand
Application Category:	Release a Qualifying Organism under the Hazardous Substances and New Organisms (HSNO) Act 1996
Purpose:	To release FluAvert® I.N., an intranasal vaccine to be used to prevent or combat an outbreak or in vaccination programmes against equine influenza
ERMA Applications Contact:	Andrea McNeill
Date:	5 December 2007
MAF Response Coordinator:	Liz Phillips
Submission Summary:	
Option to Speak in Support of this Submission:	No

BASIS ON WHICH COMMENT IS PROVIDED

MAF submits these comments for consideration to ERMA New Zealand on the following:

- The import into New Zealand of the vaccine FluAvert® I.N.

MAF does not provide comments in this submission on the scientific merit, validity or rationale of purpose of the application. These comments, if deemed necessary, will be provided via a separate submission.

Reference	Comment
1. Lincoln Broad, Senior Advisor, Risk Analysis (Animals)	Risk Analysis has previously provided advice included on page 10 of the application. In addition, we have also identified that live virus may be excreted for a short time from the recipient. Risk analysis concluded that any in-contact horse that might be infected from an excreting recipient of the vaccine would be "vaccinated" with no adverse effects likely. This has been subsequently covered in the application by others on page 11 and 14 specifically and reiterated in other parts also. For registration under the ACVM Act, a risk assessment will be required where we will investigate whether the manufacturing processes in place are effective, and what testing the company routinely does for adventitious agents.
2. Kathryn Hurr, Senior Advisor, Operations	Comments on proposed controls: 1. Section 5.3 - It may be impractical to vaccinate every horse on a

property within timeframes of a co-ordinated response. Isolation of non-vaccinated horses from vaccinated horses is a preferred alternative.

2. Section 7 - however, if it is not be possible to isolate vaccinated horses

from non-vaccinated horses, depending on the buffer zones required, then vaccination of all horses would be required.

3. Section 5.5 - Need to make the explicit connection between "correct handling procedures" and veterinary training as in section 4.

4. Section 6.3 - It may be difficult to enforce hand-washing after contact with horses for 10 days post-vaccination.

5. Section 6.4 - It may be necessary to define which "equipment" are included under this control, otherwise bridles, bits, halters and other tack could be included. Suggest changing "ie Virkon" to "eg Virkon".

6. Horses are presumably likely to sneeze during and after receiving intranasal vaccine - is disinfection of stalls or holding areas after 10 days vaccination treatment required?