For Discussion on **Discussion Paper GMO 02/2023**
24 March 2023

Genetically Modified Organisms (Control of Release) Expert Group

Review of the Exemption of Live Recombinant Veterinary Vaccines

Purpose

This paper briefs members on a review of the exemption of live recombinant veterinary vaccines in Hong Kong.

Background

2. The Genetically Modified Organisms (Control of Release) Expert Group (the Expert Group) had discussed in meetings held in 2011, 2015 and 2018 the risk assessment and disposal of live recombinant veterinary vaccines (LRVVs) in Hong Kong. The risk assessment for LRVVs indicated that they were highly unlikely to pose any risk to the biodiversity of the local environment and the possible biosafety effect of LRVVs was deemed acceptable. On the other hand, it was considered necessary to cater for the need of application of veterinary vaccines in emergency situations such as an outbreak of a pandemic disease. If not exempted, the application of such vaccines in case of emergency could be hindered by the lengthy approval process as stipulated in the Genetically Modified Organisms (Control of Release) Ordinance, Cap. 607 (the Ordinance). In this connection, the Expert Group recommended that LRVVs should be exempted from the application of section 5 (restrictions on release into environment and maintenance of lives of genetically modified organisms (GMOs)) and section 7 (restrictions on import of GMOs intended for release into the environment) of the Ordinance.

3. The Expert Group has also advised that the Agriculture, Fisheries and Conservation Department (AFCD) should also continue monitoring the latest progress and development of LRVVs and carry out a review of the exemption of LRVVs regularly for reporting to the Expert Group.

4. The Genetically Modified Organisms (Control of Release) (Exemption) Notice took effect on 23 June 2012 to exempt all varieties of LRVVs from the application of

sections 5 and 7 of the Ordinance[1].

5. AFCD conducted a review of the exemption of LRVVs and consulted the Expert Group in 2015 and 2018. The third round of review has been completed by AFCD, and the results of the review are presented in the ensuing paragraphs.

Live Recombinant Veterinary Vaccines

6. LRVVs are vaccines where a live microorganism (bacteria or virus) has been modified to express its entire genome or a portion of foreign RNA or DNA sequences or proteins and where the replicative competent vector acts as a carrier and may itself act as a protective immunogen for veterinary uses. Therefore, LRVVs are GMOs which are attenuated with definite, non-reverting mutations or deletions. The live vaccine may be a non-virulent strain expressing the antigen-encoding genes isolated from pathogenic strain(s), or it may be a pathogenic strain turned into non-virulent by selective modification or deletion of gene(s) contributing to its virulence.

7. Veterinary vaccines are pharmaceutical products that are required to be registered under the Pharmacy and Poisons Regulations Cap. 138A in order for them to be sold, offered for sale, distributed or possessed for the purposes of sales, distribution or other use in Hong Kong. Among the 18 veterinary vaccines that are currently registered in Hong Kong[2], there are 14 live vaccines, of which none of them is LRVV. However, according to Section 36(1A)(ab) of the Pharmacy and Poisons Regulations Cap. 138A, unregistered pharmaceutical products including vaccines could be possessed or used for the purpose of treatment by a registered veterinary surgeon of a particular animal. According to the importation record kept by the Department of Health, six LRVVs[3] listed in the 2018 review assessment had been imported into Hong Kong within the last 5 years.

8. Vaccination with live microorganisms may lead to the shedding or spreading of the administrated microorganisms into the environment. The shed microorganisms may grow or reproduce and bring about adverse impact on the environment. Therefore, the administration of, or import with the purpose of administration of LRVVs would in effect

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[1] Genetically Modified Organisms (Control of Release) (Exemption) Notice. https://www.elegislation.gov.hk/hk/cap607B!en@2012-08-02T00:00:00

[2] Drug Office 2023. Registered Pharmaceutical Products. Published online and continuously updated: http://www.drugoffice.gov.hk/eps/do/en/consumer/reg_pharm_products/index.html (retrieved on 2 March 2023)

[3] The six LRVVs involved seven commercial products (Purevax FeLV and Purevax RCP FeLV containing the same GMO).

be considered as release of GMOs into the environment and would be subject to the regulation under the Ordinance.

Risk Assessment of Live Recombinant Veterinary Vaccines

9. In general, regulation of LRVV is being conducted by relevant authorities through registration, risk assessments or relevant safety studies[4,5,6].

10. Risk assessment of LRVVs was previously undertaken in 2015 and 2018 to assess the possible adverse effects of LRVVs on local biodiversity. A review was conducted in March 2023 to update the list of LRVVs. The updated risk assessment report is attached at Annex.

11. The current review has covered the risk assessment of 32 LRVVs, focusing on the 11 LRVVs which have recently become commercially available and thus were not included in the previous risk assessments.

12. A number of potential adverse biosafety effects could be resulted from the administration of the LRVVs, including establishment of an undesirable self-sustaining population, altered pathogenicity or host range, horizontal gene transfer and recombination with other virus/bacteria, reversion to virulence, possibility to spread to the environment and effects on local host species.

13. All of the LRVVs assessed are non-pathogenic and attenuated with no or very limited transmission capabilities. The assessed LRVVs also showed high genetic stability. The likelihood of recombination and horizontal gene transfer is considered to be low and that of the generation of virulent strains is even lower. Based on the review, it is concluded that the potential risk to local biodiversity posed by the LRVVs is very low and the possible biosafety effect of LRVVs is deemed acceptable.

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[4] European Medicines Agency 2004. Guideline on live recombinant vector vaccines for veterinary use. EMEA/CVMP/004/04-FINAL. Accessed on 2 March 2023.

[5] National Pharmaceutical Regulatory Agency, Ministry of Health Malaysia 2023. List of renewal approved veterinary products. Accessed on 2 March 2023.

[6] United States Department of Agriculture 2023. Licensed Veterinary Biological Product Information. Accessed on 2 March 2023.

Advice Sought

14. In the light of the findings of the latest review, it is proposed that the current control and exemption for LRVVs under the Ordinance shall be maintained. Members are invited to note and provide their views on the review on the exemption of LRVVs.

Agriculture, Fisheries and Conservation Department
March 2023

Annex

Risk Assessment Report

2023

Live Recombinant Veterinary Vaccines

1. Introduction

1.1 Genetically modified or live recombinant veterinary vaccines (LRVVs) are vaccines where a live microorganism, e.g. bacteria or virus, has been modified to express entire genomes or a portion of foreign RNA or DNA sequences or proteins and where the replicative competent vector acts as a carrier and may itself act as a protective immunogen. The vaccines are attenuated and genetically defined live vaccines, which have definite, non-reverting mutations or deletions, for veterinary uses (1). In view of the rapid development in the production of LRVVs and the potential application of such vaccines in Hong Kong, a risk assessment is undertaken to assess the possible adverse biosafety effect of the live recombinant veterinary vaccines on the local environment.

1.2 This risk assessment report was prepared in accordance with Schedule 3 of the Genetically Modified Organisms (Control of Release) Ordinance Cap. 607 with respect to the requirements on risk assessment on possible adverse biosafety effects of GMOs on the local environment.

2. Identities of the GMOs

2.1 Based on the information from various sources, there are 32 commercially available LRVVs (2, 3, 4). Although this may not be an exhaustive list of such products, they include the major categories and provide a basis for a comprehensive assessment of LRVVs available. Within the 32 LRVVs, 21 listed and assessed previously in the Discussion Paper GMO/02/2018 are still currently commercially available (Table 1). Amongst them, six unregistered LRVVs were imported to Hong Kong by the registered veterinary surgeon for treatment of particular animals. The following risk assessment would focus on the LRVVs that have not been assessed previously or are newly commercialised (Table 2).

Table 1. The commercially available LRVVs listed and assessed previously (see GMO/02/2018 for more details).

#	**Commercial Name (GMO Name)**	**Target Animal**	**Target Disease**	**Parental Organism**	**Donor Organism**	**Vector**
1	Purevax ® FeLV**, ~ RCPCh FeLV, and ~ RCP FeLV (vCP97)	Cat	Feline Leukaemia	Canarypox Virus strain ALVAC (ATCC no. VR-2547)	Feline Leukaemia Virus subgroup A (strain Glasgow-1)	pBlueScript© SK+
2	Oncept IL-2 (vCP1338)	Cat	Fibrosarcoma	Canarypox Virus strain ALVAC (ATCC no. VR-2585)*	Canarypox Virus (strain NYVAC)*	pUC8
3	Purevax® Feline Rabies, ~ Feline 3/Rabies, ~ Feline 4/Rabies, and ~ Feline Rabies 3 YR (vCP65)	Cat	Rabies	Canarypox Virus strain ALVAC (ATCC no. VR-2547)	Rabies Virus (strain ERA)	pUC9
4	Bovela	Cattle	Bovine Viral Diarrhoea	Bovine Viral Diarrhoea Virus type 1 (strain KE-9) and type 2 (strain NY-93)	Nil	pXIKE-B-NdN and pKANE99C
5	Vectormune® HVT AI	Chicken	Avian Influenza and Marek's Disease	Turkey Herpesvirus (HVT)serotype 3 (strain FC-126)	Avian Influenza H5N1	rHVT/AI*
6	Vectormune ® FP MG	Chicken	Chronic Respiratory Disease and Fowlpox	Fowlpox Virus (strain FP)	*Mycoplasma gallisepticum* (strains S6 & R) and	pUC18

#	Commercial Name (GMO Name)	Target Animal	Target Disease	Parental Organism	Donor Organism	Vector
					Marek Disease Virus (serotype 1 GA)	
7	Vectormune ® FP-LT and Vectormune ® FP-LT + AE	Chicken	Laryngotracheitis and Fowlpox	Fowlpox Virus (strain Cutter)	Infectious Laryngotracheitis Virus (strain LT 632 and NS175)	pUC18
8	Vaxxitek HVT+IBD (vHVT013-69)	Chicken	Infectious Bursal Disease and Marek's Disease	HVT (strain FC-126)	Infectious Bursal Disease Virus (strain F52/70)	Unknown
9	Vectormune ® HVT-IBD	Chicken	Infectious Bursal Disease and Marek's Disease	HVT (strain FC-126)	Infectious Bursal Disease Virus (strain Delaware variant "E USA")	pUC18
10	Innovax® ILT	Chicken	Laryngotracheitis and Marek's Disease	HVT (strain FC-126)	Infectious Laryngotracheitis Virus	pNEB193
11	Innovax® ND, ~ND-IBD and ~ ND –SB (HVT/NDV-F)	Chicken	Newcastle Disease and Marek's Disease	Turkey Herpesvirus serotype 2 (strain SB-1)	Newcastle Disease Virus, (strain "clone 30")	pGEM-3Z
12	Poulvac® ST (STM-1)	Chicken	*Salmonella* Infection	*Salmonella typhimurium*, (strain 82/6915)	*Salmonella typhimurium* LT2 strain1545	Enterobacteria phage P22

#	Commercial Name (GMO Name)	Target Animal	Target Disease	Parental Organism	Donor Organism	Vector
13	Vectormune® HVT IBD & Rispens	Chicken	Infectious Bursal Disease and Marek's Disease	HVT	Infectious Bursal Disease Virus (VP2 gene of strain F52/70)	pUC18
14	Vectormune® ND	Chicken	Newcastle Disease and Marek's Disease	HVT (strain FC-126)	Newcastle Disease Virus (F gene of strain Clone 30)	pBR322 or pUC series
15	Purevax® Ferret Distemper	Ferret	Distemper	Canarypox Virus (strain ALVAC)	Canine Distemper Virus	Unknown
16	Proteqflu, Proteqflu-TE, Recombitek® Equine Influenza (vCP1529, vCP1533, vCP2422)	Horse	Equine Influenza	Canarypox Virus (strain ALVAC)	Equine Influenza H3N8 (A/Eq/Kentucky/94, A/equi-2/Newmarket/2/93, A/equine-2/Ohio/03)	pUC8
17	Recombitek® Proteq West Nile	Horse	West Nile Virus	Canarypox Virus (strain ALVAC)	Western Nile Virus (strain NY99)	pBlueScript© II SK+
18	*Rhodococcus equi* Vaccine (*R. equi* RG2837)	Horse	Pneumonia	*Rhodococcus equi*, RHOE1 (strain 103S)	Nil	pSelAct
19	PRV/Marker Gold® (S-PRV-155)	Pig	Pseudorabies	Pseudorabies Virus (strain ISU S62/26*)	Nil	pSP19, pSP65
20	Suvaxyn CSF Marker	Pig	Classical Swine Fever	Bovine Viral Diarrhoea	Classical Swine Fever Virus	pGEM-T Easy

#	Commercial Name (GMO Name)	Target Animal	Target Disease	Parental Organism	Donor Organism	Vector
				Virus	(Strain Alfort 187)	
21	Raboral V-RG®	Dog, cat, cattle, raccoon & coyotes	Rabies	Vaccinia Virus (strain Copenhagen tk- phenotype)S	Rabies Virus (strain ERA)	pBR322

*updated information

Table 2. The commercially available LRVVs not assessed previously or newly commercialised.

#	Commercial Name (GMO Name)	Target Animal	Target Disease	Parental Organism	Donor Organism	Vector
1	Prevexxion RN, ~ RN+HVT+IBD Reference: 5	Chicken	Infectious Bursal Disease and Marek's Disease	Marek's Disease Virus serotype 1 (MDV1) (strain CVI988), HVT (vHVT013-69)	MDV1 (strain RN1250), Infectious Bursal Disease Virus (IBDV) (VP2 gene)	HVT FC-126
2	Ultifend ND IBD Reference: 6	Chicken	Newcastle Disease, Infectious Bursal Disease and Marek's Disease	HVT (strain rHVT/ND/IBD)	Newcastle Disease Virus (NDV) (F gene), IBDV (VP2 gene)	Unknown
3	Innovax-ND-ILT Reference: 7	Chicken	Newcastle Disease, Infectious Laryngotracheitis (ILT) and Marek's Disease	HVT (strain FC-126)	NDV (F gene), ILT virus (gD and gI genes)	Unknown
4	Nobivac DP Plus Reference: 8	Dog	Canine Parvovirus (CPV), Canine Distemper	CPV (strain 154)	CPV (strain 630a)	p630a
5	Nobivac Myxo-RHD Plus Reference: 9	Rabbit	Myxomatosis and Rabbit Haemorrhagic Disease (RHD)	RHD virus 1 & 2	Myxoma Virus (strains 009 & MK1899)	Unknown

#	Commercial Name (GMO Name)	Target Animal	Target Disease	Parental Organism	Donor Organism	Vector
6	Rift Valley Fever Virus DIVA vaccine Reference: 10, 11	Sheep, goats, cattle	Rift Valley Fever	Chimpanzee Adenovirus Y25 (deletion of gene E1)	Rift Valley Fever Phlebovirus	ChAdOx1
7	Swine Influenza Virus vaccine Reference: 12	Pig	Swine Influenza	Influenza A Virus (H1N1, H3N2)	Nil	pHW2000
8	Prime Pac® PRRS RR Reference: 13, 14, 15	Pig	Porcine Reproductive & Respiratory Syndrome (PRRS)	PRRS virus (vFL12, vPP18, Neb-1)	Unknown	Unknown
9	FLEX CircoPRRS (Ingelvac CircoFLEX® + Ingelvac PRRS® MLV) Reference: 16, 17	Pig	Porcine Circovirus-associated Disease, PRRS	PRRS virus	Unknown	Unknown
10	Bovilis Nasalgen 3, ~3-PMH (for intranasal use) References: 18, 19	Cattle	Infectious Bovine Rhinotracheitis (IBR), Bovine Respiratory Syncytial Virus (BRSV), Parainfluenza (PI_3), *Pasteurella multocida* (PM) and *Mannheimia*	IBR virus, BRSV, PI_3 virus, PM and MH	Unknown	Unknown

#	Commercial Name (GMO Name)	Target Animal	Target Disease	Parental Organism	Donor Organism	Vector
			haemolytica (MH)			
11	Stimulator® IBR, 2, ~2+BRSV, ~3, ~5 Reference: 20	Cattle	IBR, BRSV, PI_3, Bovine Viral Diarrhea (BVD)	IBR virus, BRSV, PI_3 virus, BVD virus 1 & 2	Unknown	Unknown

3. Recipient/parental Organisms

3.1 Marek's Disease Virus - (for vaccine # 1 - 3)

Marek's Disease Virus (MDV) is a double-stranded DNA virus with no RNA intermediate, belonging to the genus *Mardivirus* that includes three species or serotypes designated as *Gallid herpesvirus* 2 (Rispens) (serotype 1), *Gallid herpesvirus* 3 (SB-1) (serotype 2) and *Meleagrid herpesvirus* 1 or *herpesvirus* of turkeys (HVT or MDV-3) (serotype 3). HVT, or Turkey Herpesvirus, contains naturally avirulent strains (e.g. FC-126, HVP360) and is used as a recombinant viral vaccine vector and vaccine against Marek's Disease (7). The viral vectors do not revert to virulence and are species-specific, such that they are not likely to be transmitted to or replicate in other hosts (21).

3.2 Canine Parvovirus – (for vaccine # 4)

Canine Parvovirus (CPV) is a highly contagious viral disease of dogs that commonly causes acute gastrointestinal illness. The CPV strain 630a has the same attenuating backbone and capsid amino acid changes as canine parvovirus strain 154, which has a history of safe use for more than 25 years (8). There are no indications that recombination or reversion to virulence occurs under field conditions. (8)

3.3 Myxoma Virus and Rabbit Haemorrhagic Disease Virus – (for vaccine # 5)

Both Myxomatosis and Rabbit Haemorrhagic Disease (RHD) are highly contagious and fatal diseases in rabbits. The active substances in the vaccine are two live recombinant myxoma-vectored RHD viruses (strain 009 and strain MK1899), expressing the capsid protein gene of classical (type 1) or type 2 RHD viruses respectively, which trigger an active immune response against both myxoma and RHD viruses (9).

3.4 Chimpanzee Adenovirus – (for vaccine # 6)

Rift Valley Fever is an acute viral disease commonly seen in domesticated animals, such as sheep, goat, cattle, buffalo and camel. It also has the capacity to infect humans. Chimpanzee Adenovirus Oxford 1 (ChAdOx1) is a replication-deficient vaccine vector derived from Chimpanzee Adenovirus Y25 and contains a deletion of the gene responsible for replication, E1 (10).

3.5 Influenza A Virus in swine – (for vaccine # 7)

Influenza A is a type of virus that causes the flu in birds and some mammals such as pig. The vaccine contains two modified virions, H1N1 and H3N2, for developing immunity to both viruses (12).

3.6 Porcine Reproductive & Respiratory Syndrome Virus – (for vaccine # 8 - 9)

The porcine reproductive & respiratory syndrome virus (PRRSV) is a highly pathogenic RNA virus that can cause late-term reproductive failure and severe pneumonia in neonatal pigs.

3.7 Infectious Bovine Rhinotracheitis Virus, Bovine Respiratory Syncytial Virus, Parainfluenza Virus, *Pasteurella multocida* (PM) and *Mannheimia haemolytica* (MH), Bovine Viral Diarrhea Virus – (for vaccine # 10 - 11)

Infectious Bovine Rhinotracheitis Virus (IBRV) causes in cattle a severe disease predominantly in the upper respiratory tract, while Bovine Respiratory Syncytial Virus and parainfluenza virus are closely related viruses involved in Bovine Respiratory Disease (BRD). The bacteria *Pasteurella multocida (PM) and Mannheimia haemolytica (MH)* are also major agents of respiratory disease in cattle. Lastly, Bovine Viral Diarrhea Virus (BVDV) is an RNA virus that includes two genotypes, types 1 and 2, resulting in enteric, respiratory, and/or reproductive disease of cattle.

4. Donor Organisms

4.1 Turkey Herpesvirus - (for vaccine # 1)

Turkey Herpesvirus, or HVT, contains naturally avirulent strains (e.g. FC-126) and is used as a recombinant viral vaccine vector and vaccine against Marek's Disease (7).

4.2 Infectious Bursal Disease Virus - (for vaccines # 2 – 3)

The Infectious Bursal Disease Virus (IBDV) is a double-stranded RNA virus in the genus *Avibirnavirus* that includes two serotypes, causing Infectious Bursal Disease (IBD), also known as Gumboro Disease. The disease would lead to lymphoid depletion of the bursa and immune-depression and cause secondary infections. Although turkeys, ducks, guinea

fowls and ostriches may be infected, clinical disease occurs solely in chickens (22).

4.3 Newcastle Disease Virus - (for vaccines # 3)

Newcastle Disease (ND) is a contagious and fatal viral disease that affects the respiratory, nervous and digestive systems of birds and poultry. ND can present a clinical picture very similar to avian influenza, so laboratory testing is important to confirm the diagnosis (23).

4.4 Laryngotracheitis Virus - (for vaccine # 3)

Infectious Laryngotracheitis (ILT) is an acute, highly contagious respiratory disease of chickens, caused by Infectious Laryngotracheitis Virus (ILTV). ILTV is a DNA virus that can affect pheasants, partridges and peafowl with high morbidity and moderate mortality, yet there is no known risk of human infection (24).

4.5 Canine Parvovirus - (for vaccine # 4)

Canine Parvovirus is a highly contagious virus that affects dogs' gastrointestinal tracts and is spread by direct dog-to-dog contact and contact with contaminated faeces, environments, or people (25).

4.6 Myxoma Virus - (for vaccine # 5)

Myxomatosis is a rabbit disease caused by a poxvirus, Myxoma Virus (MV). It is spread through fleas and mosquitoes that ingest the virus while biting infected animals then transmit the disease to other susceptible animals (26).

4.7 Rift Valley Fever *Phlebovirus* – (for vaccine # 6)

Rift Valley Fever (RVF) is an acute viral hemorrhagic fever that is most commonly seen in domesticated animals, caused by RVF virus, a member of the genus *Phlebovirus*.

5. Vectors

5.1 p630a (for vaccine # 4)

The production process of the CPV component starts with a transfection step, i.e. deliberately introducing naked or purified nucleic acids into eukaryotic cells, with plasmid

p630a. The parvovirus strain was replaced with Canine Parvovius strain 630a. CPV630a was shown to have disseminated to various tissues within four days of administration and the virus could not be detected in the same tissue types 11 days post administration due to neutralizing levels of antibodies. (8).

5.2 pHW2000 (for vaccine # 7)

The plasmid pHW2000 is derived from pHW12. The cloning vector contains promoter and terminator sequence separated by two BsmBI sites. After digestion of the Polymerase Chain Reaction (PCR) products with BsmBI, the fragments of eight cDNAs were cloned into the vector pHW2000. The transfection of the eight expression plasmids allows the recovery of an Influenza A Virus (12).

6. Insert and Modification

6.1 Prevexxion RN, ~ RN+HVT+IBD # 1

RN1250 is an engineered Marek's Disease Virus based on the MDV CVI988 parental vaccine virus that contains two copies of Reticuloendotheliosis Virus long terminal repeats from MDV RM1 strain inserted in its genome. The RN1250 recombinant virus was generated by *in vitro* homologous recombination between CVI988 and a cosmid containing a genomic fragment of RM1 and of Md5 MDV1 strains (5).

6.2 Ultifend ND IBD # 2

This vaccine contains a live recombinant HVT which is genetically modified to express the fusion (F) gene of NDV and the virion protein (VP2) of IBDV, inducing active immunity against Newcastle Disease, Infectious Bursal Disease and Marek's Disease (6).

6.3 Innovax-ND-ILT # 3

A HVT vaccine strain (HVT FC-126) is genetically modified by insertion of the NDV F gene and the ILT gD and gI genes and regulatory sequences, to generate HVT/NDV/ILT (7).

6.4 Nobivac DP Plus # 4

Vaccine strain CPV630a is a hybrid virus that was derived from the backbone of the existing

vaccine virus strain 154 and the attenuated capsid of a currently circulating type 2c isolate. The virus was constructed using molecular cloning techniques, but does not contain any exogenous 'non-canine parvovirus' genetic material (8).

6.5 Nobivac Myxo-RHD Plus # 5

This vaccine contains live myxoma virus which has been modified to produce proteins from the outer coat of either RHDV1 (strain 009) or RHDV2 (strain MK1899) (9).

6.6 Rift Valley Fever Virus DIVA vaccine # 6

ChAdOx1 is a replication-deficient vaccine vector and contains a deletion of the gene, E1, which is responsible for replication (10).

6.7 Swine influenza virus vaccine # 7

After digestion of the PCR products with BsmBI, the fragments of eight cDNAs were cloned into the vector pHW2000 (12).

6.8 Prime Pac® PRRS RR # 8

Relevant information is not available.

6.9 FLEX CircoPRRS # 9

Relevant information is not available.

6.10 Bovilis Nasalgen 3, ~3-PMH (for intranasal use) # 10

Relevant information is not available.

6.11 Stimulator® IBR, 2, ~2+BRSV, ~3, ~5 # 11

Relevant information is not available.

7. Differences between the Biological Characteristics of the GMO and those of the Recipient or Parental Organism

7.1 Vaccines using Marek's Disease Virus as parental organisms - # 1 - 3

The GM vaccines differ genetically from the parental HVT by the integration of the

expression cassette which contains i) the gene encoding the VP2 structural protein of IBDV and a stop codon, ii) the insertion of fragment of NDV containing F gene and the respective promoter region, or iii) the insertion of two genes, *gD* and *gI*, of a ILTV with their respective endogenous ILTV promoters and single shared endogenous polyadenylation signal. The foreign DNA has been inserted into a non-coding region of the HVT genome. Both the parental strain and the GMO were found to be non-pathogenic to the host and were not transmitted from infected birds to the un-infected birds. The host range, tissue tropism, and shedding or spreading capabilities of the recombinant organism are expected to be similar to the parental HVT vaccine strain (5, 6, 7).

7.2 Canine Parvovirus as parental organisms - # 4

Nobivac DP Plus is a lyophilised live vaccine, containing Canine Distemper Virus strain Onderstepoort which is a conventionally attenuated live vaccine strain and Canine Parvovirus (CPV) strain 630a which is a genetically modified hybrid CPV strain. Vaccine strain CPV630a is a hybrid virus that was derived from the backbone of the existing vaccine virus strain 154 and the attenuated capsid of a currently circulating type 2c isolate (8).

7.3 Myxoma Virus and Rabbit Haemorrhagic Disease Virus as parental organisms - # 5

The active substances in the vaccine are two live recombinant RHD viruses (strain 009 and strain MK1899), expressing the capsid protein gene of classical (type 1) or type 2 RHD viruses respectively, which trigger an active immune response against both Myxoma and RHD viruses (9). The vaccine does not adversely affect the immunological functions as two main virulence factors are deleted from the Myxoma vector genome (9).

7.4 Chimpanzee Adenovirus as parental organisms - # 6

Vector derived from Chimpanzee Adenovirus contains a deletion of the gene responsible for replication, E1. The modified adenovirus is not expected to replicate within the animal (10).

7.5 Influenza A Virus as parental organisms - # 7

The vaccine contains two modified virions, H1N1 and H3N2, with eight expression plasmids transfected to allow the recovery of an influenza A Virus (12).

7.6 Porcine Reproductive & Respiratory Syndrome Virus as parental organisms - # 8 - 9

Relevant information is not available.

7.7 Infectious Bovine Rhinotracheitis Virus, Bovine Respiratory Syncytial Virus, Parainfluenza Virus, *Pasteurella multocida* (PM) and *Mannheimia haemolytica* (MH), Bovine Viral Diarrhea Virus as parental organisms - # 10 – 11

Relevant information is not available.

8. Detection and Identification of the GMO

As the DNA sequences involved in the genetic modifications are readily accessible in some literature, the GMOs can be detected and identified with high sensitivity by PCR. For vaccines # 8 – 11, the DNA sequence is not available likely due to commercial reasons.

9. Intended Use of the GMO

The GMOs are used as main active components of the veterinary vaccines for vaccination against diseases listed in Table 2.

10. Likely Potential Receiving Environment

10.1 Vaccine using Marek's Disease Virus as parental organism - # 1 - 3

The GM vaccines are intended for mass administration to chickens for prevention of diseases and so they are likely to be used in commercial poultry farms. The genetic modifications are unlikely to change the host range, mode of transmission or their non-pathogenic nature.

10.2 Canine Parvovirus as parental organisms - # 4

The GM vaccine is intended for pet dogs (puppies from 4 weeks of age onwards) to prevent

clinical signs and mortality of CPV infection. The dose is likely to be used at veterinary clinics or relevant animal keeping facilities, e.g. dog kennels and dog shelters.

10.3 Myxoma Virus and Rabbit Haemorrhagic Disease Virus as parental organisms - # 5

The GM vaccine is intended for pet rabbits (from 5 weeks of age onwards) to reduce mortality and clinical signs of myxomatosis and RHD. The dose is likely to be used at veterinary clinics, rabbit farms or relevant animal keeping facilities.

10.4 Chimpanzee Adenovirus as parental organisms - # 6

The GM vaccine is intended for livestock, such as sheep, goats, cattle and dromedary camels so it is likely to be used in commercial goat and dairy farms.

10.5 Influenza A Virus as parental organisms - # 7

Influenza A Virus can cause swine influenza in pigs. The GM vaccine is likely to be used in commercial pig farms, yet it can also be potentially used to vaccinate birds and a variety of mammals.

10.6 Porcine Reproductive & Respiratory Syndrome Virus as parental organisms - # 8 - 9

The GM vaccine is likely to be used in commercial pig farms.

10.7 Infectious Bovine Rhinotracheitis Virus, Bovine Respiratory Syncytial Virus, Parainfluenza Virus, *Pasteurella multocida* (PM) and *Mannheimia haemolytica* (MH), Bovine Viral Diarrhea Virus as parental organisms - # 10 – 11

The GM vaccine is likely to be used in commercial dairy farms.

11. Identification of any Novel Genotypic and Phenotypic Characteristics Associated with the GMO that may have an Adverse Effect on Biological Diversity in the Likely Potential Receiving Environment

The potential adverse effects associated with the novel genotypic characteristics of LRVVs may include:

1. Establishing an undesirable self-sustaining population
2. Altered pathogenicity or host range
3. Horizontal gene transfer and recombination with other virus / bacteria
4. Reversion to virulence
5. Possibility to spread to the environment
6. Effects on local host species

12. Evaluation of the Likelihood of the Adverse Effect Being Realised

GM vaccines / Adverse effects	12.1 With GM MDV (#1–3)	12.2 With GM CPV (#4)	12.3 With GM Myxoma Virus and RHDV (#5)	12.4 With GM Chimpanzee Adenovirus (#6)	12.5 With GM Influenza A Virus (#7)	12.6 With GM PRRSV (#8-9)	12.7 With GM IBRV, BRSV, Parainfluenza Virus, PM and MH, BVDV (#10-11)
Establishing an undesirable self-sustaining population	No differences observed between the initial and the in vitro passaged viral populations (5)	N/A	N/A	N/A	Risk of wild uncontrolled growth is low (27)	N/A	N/A
Altered pathogenicity or host range	Intrinsic pathogenicity was not increased (5, 6)	The insertion of genes has not altered the host range (7)	N/A	A switch in host range is considered unlikely (9)	The risk of pathogenicity occurring is negligible (27)	N/A	N/A
Horizontal gene transfer and recombination	Recombination events with viruses replicating	The risk of recombination and/or genomic	There is no indications that recombination	No reports suggested a recombination and	Risk of transfer of ChAdOx1- Gn-Gc to unvaccinated	N/A	Stability and purity are tested and confirmed to

with other virus / bacteria	RNA are highly unlikely (6)	reassortment is effectively zero (7)	occurs under field conditions (8)	the risk of reassortment is considered as very low (9)	animals is low (27)		ensure no mutation in viral antigens. No extraneous, unwanted viruses are introduced (20)
Reversion to virulence	The possible reverse interference does not appear to be biologically significant (5) or was not observed (6)	The potential risk of reversion to virulence is low and acceptable (7)	No reversion of virulence after being backpassaged could be demonstrated (8)	No indication of reversion to virulence was noted (9)	There is no report of reversion to replication competency of vaccine vectors (27)	No danger of reversion to virulence (17)	N/A
Possibility to spread to the environment	There was no spread to contacts (5, 6)	No evidence of spread and dissemination of the vaccine was obtained (7)	There was no spread to the in-contact dog, but vaccine virus spreading via faeces was shown (8)	The potential risk of the product to the environment and associated level of risk is estimated as zero (9)	The vaccine vector is not capable of persisting in the environment (27), so it is not possible to spread to the environment.	No potential for it to combine with field strains (17)	N/A

Effects on local host species	The risk to local animals is very low	The risk to local animals is very low	The risk to local animals is very low	The risk to local animals is very low	The risk of the inserted genes causing adverse effects on non-targets is negligible (27)	N/A	N/A

13. Evaluation of the Consequences should the Adverse Effect be Realised

13.1 Establishing an undesirable self-sustaining population

As the vaccines are not pathogenic and some of them are not viable in the wild environment, establishment of an undesirable self-sustaining population should not result in significant adverse effect on Hong Kong's biodiversity.

13.2 Altered pathogenicity or host range

If the host range is changed, there might be adverse effects on Hong Kong's biodiversity as the pathogenicity on different hosts may be different. Since the genes modified are not relevant to the host range, it is expected that the genetic modification would not change the host range. Hence, they shall not result in significant adverse effect on Hong Kong's biodiversity.

13.3 Horizontal gene transfer and recombination with other viruses / bacteria

If horizontal gene transfer and recombination with other viruses / bacteria occur, the chance to produce viral or bacterial strains with severe pathogenicity shall not be different from those happening among non-GM strains.

13.4 Reversion to virulence

As the diseases are already present in nature, the reversion to virulence shall not result in significant adverse effect on Hong Kong's biodiversity.

13.5 Possibility to spread to the environment

As most target animals are domesticated, spreading to the environment would be limited. The GMOs are assessed to be mostly non-transmissible, and are less transmissible than the parental strains. And as the diseases are already present in nature, the spreading of the non-pathogenic vaccine strains to the environment shall not result in any significant adverse effect on Hong Kong's biodiversity.

13.6 Effects on local host species

As the vaccines are not pathogenic, adverse effect on local host species is not anticipated.

14. Estimation of the Overall Risk Posed by the GMO

14.1 Vaccines using Marek's Disease Virus as parental organism - # 1 - 3

Since the parental strain for the GMO is a non-pathogenic strain, the risk of the LRVVs to the local biological diversity is considered low and acceptable.

14.2 Vaccine using Canine Parvovirus as parental organisms - # 4

The parental strain for the GMO is an attenuated strain. The risk of the LRVV to local biodiversity is thus considered low and acceptable.

14.3 Vaccine using Myxoma Virus and Rabbit Haemorrhagic Disease Virus as parental organisms - # 5

The GMO in this LRVV is non-pathogenic and not transmissible. The risk of the LRVV to local biodiversity is thus considered low and acceptable.

14.4 Vaccine using Chimpanzee Adenovirus as parental organisms - # 6

The GMO in this LRVV is not transmissible. The risk of the LRVV to local biodiversity is thus considered low and acceptable.

14.5 Vaccine using Influenza A Virus as parental organisms - # 7

The GMO in this LRVV is not transmissible. The risk of the LRVV to local biodiversity is thus considered low and acceptable.

14.6 Vaccines using Porcine Reproductive & Respiratory Syndrome Virus as parental organisms - # 8 - 9

The GMO is not transmissible. The risk of the LRVVs to local biodiversity is thus considered low and acceptable.

14.7 Vaccines using Infectious Bovine Rhinotracheitis Virus, Bovine Respiratory Syncytial Virus, Parainfluenza Virus, *Pasteurella multocida* (PM) and *Mannheimia haemolytica* (MH), Bovine Viral Diarrhea Virus as parental organisms - # 10 – 11

The GMO is tested stable. The risk of the LRVVs to local biodiversity is thus considered low and acceptable.

Agriculture, Fisheries and Conservation Department

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