OIA18-0318

30 MAY 2018

Rachel Maria Stedman
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Dear Rachel Maria Stedman

OFFICIAL INFORMATION ACT REQUEST

I refer to your official information request on 5 March 2018 relating to information on RHDV1-K5. Unfortunately we encountered technical issues with our FYI website function which resulted in the late receipt of your request and I apologise on behalf of MPI for the delay.

Efficacy of Cylap RCD vaccine against RHDV1-K5 strain

The following information was used to assess the efficacy of the vaccine Cylap Rabbit Calicivirus Disease (RCD) against the virus RHDV1-K5. Please note, application documentation and evidential documentation have been withheld pursuant to the following sections of the Official Information Act 1982 (OIA):

- Section 9(2)(b)(ii) – to protect information where making available of the information would be likely unreasonably to prejudice the commercial position of the person who supplied or who is the subject of the information.

- Section 9(2)(ba)(i) – to protect information which is subject to an obligation of confidence or which any person has been or could be compelled to provide under the authority of any enactment, where the making available of the information would be likely to prejudice the supply of similar information, or information from the same source, and it is in the public interest that such information should continue to be supplied.

Effective and efficient regulation of registrations under the ACVM depend on a high degree of cooperation from the registrants that goes over and above compliance with minimum regulatory requirements. The Ministry for Primary Industries (MPI) consider the release of the application information would undermine the level of cooperation in a way that reduces MPI's ability to regulate effectively.

Further information on the background, testing and supporting documents surrounding the application is attached as an appendix. Emails in relation to the discussions had

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surrounding the evidence supporting the approval of RHDV1-K5 and efficacy of the vaccine also exist, however, the information contained in the emails have been disclosed in the content of your response.

MPI is satisfied that in the circumstances of this case, the withholding of the information is not outweighed by other considerations which render it desirable in the public interest to make the information available. You have the right under section 28(3) of the OIA to seek an investigation and review by the Ombudsman of our decision to withhold some information.

Yours sincerely

Allan Kinsella
Director Assurance

Appendix One

Background

RHDV1 is already widespread within the New Zealand wild rabbit population following the release of RHDV1 Czech v351 strain in 1997. At the time of release, the virus was effective at reducing rabbit numbers. In most wild rabbit populations, RHDV1 Czech v351 continues to be an effective bio-control; it has been found however that exposure to the benign Non-Pathogenic Australian Rabbit Calicivirus (RCV-A1) strain, and the antibody response to infection that develops, gives protection against RHDV1 Czech v351.

Recent studies undertaken at 14 different sites across New Zealand demonstrated that 21.4% of wild rabbits tested had antibodies against RCV-A1 and would therefore not be controlled by the current RHDV1 Czech v351 strain.

RHDV1-K5 was selected for improved wild rabbit bio-control due to its increased potency (requires 30 times less viral particles to kill wild rabbits compared to RHDV1 Czech v351) and because it can overcome the protective effects of RCV-A1 strain antibodies. This means the RHDV1-K5 strain requires fewer infective doses to achieve adequate control of the wild rabbit population.

Although these differences make the K5 strain a more effective bio-control, it has similar immunogenicity, host specificity, pathogenicity, morphology and genetics to the Czech v351 strain as outlined below. The introduction of RHDV1-K5 is not expected to result in the dramatic die-off observed with the release of RHDV1 Czech v351, however a controlled release at the optimum time of year in association with secondary forms of rabbit control should reduce increasing wild rabbit numbers.

The applicant provided scientific evidence to support equivalence between RHDV1 Czech v351 and RHDV1 K5 in *Deviation from the ACVM standard for Efficacy and Animal Welfare guidance documents to support importation and use of RHDV1 K5 to infect wild rabbits in New Zealand* (DV 735). The scientific evidence was accepted and approved during the assessment of DV 735. The information provided demonstrated that RHDV1 v351 and RHDV1 K5 have similar genetics, morphology, mode of action, pathogenicity, immunogenicity and host specificity.

DV 735 states the following:

"RHDV1 K5 and RCD (RHDV1 Czech v351) are RNA viruses belonging to the family Caliciveridae and the genus lagovirus. Currently 3 distinct species of lagovirus are known. These include rabbit haemorrhagic disease virus 1 (RHDV1), rabbit haemorrhagic disease virus 2 (RHDV2) and European brown hare syndrome virus (EBHSV). All represent distinct agents which infect specific animal species. Research has identified that RHDV1 (which include both RCD and K5 variants) can be divided in six genogroups and other non-pathogenic or benign caliciviruses. Phylogenetic analyses of pathogenic RHDV strains show three distinct groups which include "classica" RHDV1 (genogroups 1-5), the antigenic variant RHDV1a (genogroup 6) and RHDV2".

Both RHDV1 Czech v351 and RHDV1 K5 belong to the same serotype of the RHDV1 sub-family. RHDV1 Czech v351 is the "classical" RHDV1 (G2) genotype and RHDV1 K5 is an RHDV1a (G6) genotype. Capucci *et al* 1998 and Schirrmeier *et al* 1999 are referenced by the applicant as both papers demonstrate that monoclonal antibodies which confer protection to experimentally infected rabbits against "classical" RHDV1 genotypes also protect rabbits against RHDV1a isolates.

The papers referenced are publically available and their full titles are:

Schirrmeier H, Reimann I, Kollner B, Granzow H, 1999. *Pathogenic, antigenic and molecular properties of rabbit haemorrhagic disease virus (RHDV) isolated from vaccinated rabbits: detection and characterization of antigenic variants.* Arch Virol, 144:719-735.

Capucci L, Fallacara F, Grazioli S, Lavazza A, Pacciarini ML, Brocchi E, 1998. *A further step in the evolution of rabbit hemorrhagic disease virus: the appearance of the first consistent antigenic variant.* Virus Res, 58: 115-126. 46.

The study by Schirmeier *et al* used the Eisenhuttenstadt, Hagenow, Wriezen, Meiningen, Hartmannsdorf, Triptis and Frankfurt strains of the virus to demonstrate that vaccination with one strain will induce an antibody response that gives protection against other strains. The applicant was asked to confirm which strains in the Schirrmeier study were "classical" strains and which were RHDV1a strains since the article mentioned them in terms of strain names and not genotype.

The applicant stated the following, which is based on the analysis of genetic sequences:

"Classical" RHDV1 strains: Eisenhuttenstadt, Hagenow, Wriezen, Meiningen and Frankfurt isolates appear to be characteristic of classical RHDV1 strains displaying high (92.5-100%) homology with the amino acid region 344 and 370 of the reference strain.

RHDV1a strains: Triptus, Hartmannsdorf. Rabbits were vaccinated with inactivated preparation containing the Eisenhuttenstadt strain (RHDV1 or "classical" strain).

Following vaccination, both immunized and non-immunized rabbits were challenged with one of each of the above mentioned 6 strains (not Eisenhuttenstadt), i.e. were challenged with both VHDV1 and VHDV1a strains. No vaccinated animals showed clinical signs of disease whilst all control animals died. This study gives evidence that vaccines containing "classical" strain antigen such as "Cylap RCD Vaccine" will protect rabbits exposed to RHDV1a virus such as K5.

Capucci *et al* outlined a study where two groups of four rabbits were treated with a vaccine containing RHDV1 antigen, then inoculated (25 days post-vaccine) with one of two RHDV1a variants. None of the vaccinated rabbits demonstrated clinical signs of disease following exposure to the virus, while all four unvaccinated rabbits (two groups of two rabbits – each group exposed to one of the two RHDV1a variants) died of rabbit haemorrhagic disease (RHD) within 60 hours of exposure (no data shown). This study demonstrated that vaccination using an RHDV1 strain invokes immunity

against an RHDV1a strain of virus and supports the concept that Cylap RCD Vaccine will be efficacious in protecting vaccinated rabbits against RHDV1 K5.

Given that RCD and RHDV1 K5 invoke similar immune responses following infection, it is accepted that this is supportive of Cylap RCD Vaccine efficacy against RHDV1 K5. Whilst not confirmed by the registrant, amino acid sequencing undertaken on the vaccine suggest that the vaccine contains an RHDV1 "classical" genotype strain.

The applicant was asked to cover off duration of immunity of the current vaccine with regard to the K5 virus. The applicant argued that the above study is relevant to both the RHDV1 Czech v351 strain and the RHDV1 K5 strains given that exposure to either strain induces similar immunity and cross protection. There are currently no known studies/trials that the assessor is aware of which demonstrate that duration of immunity following vaccination will be the same for K5 as it is for the Czech strain.

The only conclusion that can be drawn from the current Australian situation is that vaccination with Cylap appears to give at least 6 months immunity. This is based on the fact that no cases of K5 in vaccinated rabbits have been reported in Australia since its release almost a year ago, and because the recommended (off-label) vaccination regime in that country is every 6 months (due to the appearance of RHDV2).

Expert advice was sought from an MPI employed virologist with regard to the duration of immunity that could be expected with the Cylap RCD vaccine against the K5 strain. Using a partial amino acid sequence of the capsid protein (VP60) used in the vaccine, the virologist was able to elucidate the following information:

"The conservation of the capsid amino acid sequence looks really solid, there are switches between RHDV1 and RHDV1a isolates that are consistent and nearly every amino acid switch is biochemically conservative. So the Cylaps vaccine is a great match for NZ and Australia RHDV1 isolates. The capsid sequence for the RHDV1a strains including the K5 exotoxin isolate are also consistent with each other, so the Cylaps vaccine will provide the same level of protection to K5 as it does to other RHDV1a isolates. I think that there is no issue here, Cylaps looks a capable candidate vaccine.

Many pet rabbits will be entirely naïve, so single immunisation might not be adequate if there is a controlled release in the locality. As the vaccine is inactivated antigen, to be safe a prime boost is a better way to go if there is a possibility of contact with a high dose of K5. The annual booster will be adequate after the initial immunisation regime".

This information gives confidence that based on amino acid sequencing, not only is the Cylap RCD vaccine considered an appropriate vaccine to induce protection in vaccinated rabbits against disease caused by exposure to K5, but it also gives confidence that the vaccine will give the same duration of immunity for the v351 and K5 strains.

Efficacy of a commercial vaccine against different strains of rabbit haemorrhagic disease virus

This study was undertaken in Australia to investigate the efficacy of a currently registered vaccine CYLAP HVD (same as the New Zealand registered Cylap RCD vaccine) and its ability to protect rabbits from disease caused by two different RHDV1 strains, Czech v351 and K5.

Results

All vaccinated rabbits demonstrated detectable antibodies against RHDV1 prior to exposure to one of the two strains of virus. None of the vaccinated rabbits died or showed any clinical signs of infection following exposure to high doses of either the v351 or K5 strains by either method of infection.

Seven of the eight unvaccinated controls died following exposure to the two viral strains. Of the two controls exposed to v 351 infected liver, one rabbit died 72-96 hours post-exposure while the second rabbit survived until it was euthanized at seven days after exposure. Both unvaccinated rabbits exposed to v351 by the oral route died between 48 and 72 hours after viral exposure. Both control rabbits exposed to K5 infected liver died between 72 and 96 hours post exposure. Both control rabbits exposed to an oral dose of K5 died between 48 and 96 hours after dosing.

Very high levels of RHDV RNA were detected by PCR method in liver samples from all the unvaccinated rabbits that died. This supports that the rabbits died of RHDV infection. The one unvaccinated rabbit exposed to K5 liver that survived for 7 days, had moderate levels of RHDV RNA livers detected in its liver. This rabbit may have become infected with a sub-lethal dose due to insufficient exposure, allowing an immune response sufficient to overcome infection. On the other hand, the rabbit may have avoided early exposure to infection, in which case, had the trial continued for longer, the rabbit may have succumbed to infection. RHDV RNA was detected in nine of the vaccinated rabbits at levels much lower than the controls.

Discussion

The applicant was asked to compare the inoculation exposure doses used in the trial with expected exposure doses in the field and if lower in the trial, to discuss whether larger doses could potentially overcome vaccine immunity and result in disease in the animal.

The applicant replied with expert opinion provided who stated the following:

"It is extremely unlikely that rabbits under field conditions would ever get exposed to a dose as high as 10,000 RID50.

Exposure/transmission in the field is predominantly believed to be occurring either via direct contact and shed virus from other rabbits, or mechanical insect transmission via flies. Asgari et al 1998 estimates the amount of virus in a fly spot to be approximately 2-3 RID50, so 3000-5000 times lower than the experimental K5 inoculum.

The genome copies of the RHDV-Czech (batch 1c) virus stock have been previously quantified using qRT-PCR, and in this case 3000 RID50 were equal to 3x 10e8 RHDV capsid gene copies. Rabbits experimentally infected with the Czech strain were shown to shed approximately 10e6 capsid copies/gram faeces prior to death (Strive et al 2010). If the ratio of infectious particles to genome copies is similar across various tissues and virus preparations, this would mean approximately 10 RID50/gram faeces, or 10,000 RID50 per kg of rabbit faeces. It is also likely that the ratio between infectious particles and genome copies is worse in rabbit or fly excreta compared to a fresh, highly concentrated and purified virus preparation

Based on these examples it is extremely unlikely that rabbits under field conditions would ever get exposed to a dose as high as 10,000 RID50."

From the above information, pet rabbits are expected to be most likely exposed to the virus either by direct contact with other infected rabbits, or by flies carrying infected rabbit faecal matter (although other methods of exposure are known such as infected hay). The amount of virus contained within a fly spot has been estimated as 2-3 RID50.

It is therefore concluded that the amount of virus used in the study was well in excess of what is likely to occur under field conditions. This gives confidence that the study used appropriate infective doses to test the vaccine efficacy.

From the information submitted, it was not immediately clear how the rabbits in the trial were monitored for signs of disease, or whether any adverse events occurred. Communication via the applicant was initiated with the study director who confirmed that rabbits were checked visually twice daily during the study and that no adverse events were noted. Food and water intake and body temperatures were not monitored during the trial. This is considered appropriate since the study was undertaken to assess vaccine efficacy rather than to identify clinical signs of disease.

Calculations of the preventable fraction:

V351 oral route = 100%

V351 liver exposure = 50%

K5 oral = 100%

K5 liver = 100%

Overall average preventable fraction 87.5% which meets the ACVM required minimum preventable fraction of 80%.

Conclusion

The study was undertaken in the target animal species and under conditions made as similar as possible to field conditions. It is accepted in this case that field conditions could not be met since the K5 virus had not been released in Australia at the time of the trial. Gaps in this area can be covered off by the adverse event reporting that has been given as part of this application since the virus was released in Australia (see below).

This study was undertaken in Australia to help meet regulatory obligations in that country and does not meet all requirements set out in the ACVM Vaccine efficacy or Research Standards. However, the information reported can be used to as supportive of Cylap RCD efficacy against the RHDV1a K5 strain in vaccinated rabbits. Other information gathered, and reported above, has helped bridge gaps in ACVM requirements that this study did not meet.

Australian information since release of RHDV1 K5

The Australian situation is somewhat different to New Zealand due the recent emergence of RHDV2 in Australia, which is not present here. Because no vaccine with specific efficacy against RHDV2 has been available in Australia, The AVA recommended an off label, intensive vaccine protocol for Cylap-HVD (The same formulation as the Cylap RCD registered in New Zealand). It is not known to what extent this confers protection against RHDV2. The suggested protocol is as follows: kittens - 4, 8 and 12 weeks of age, then every 6 months; adults two vaccines one month apart, then every 6 months.

Zoetis Australia, the supplier of Cylap RCD, has stated that adverse event reporting rate has not changed since the release of RHDV1 K5 in Australia. They also state that no adverse events have been related to inefficacy of the vaccine.

Veterinary Virologist, NSW DPI, Biosecurity NSW: Reported that prior to the release of RHDV1 K5, they had a number of cases of dead rabbits that were reported to be vaccinated where RHDV2 was detected to be present. Since the release they have not had any cases of RHDV detected in vaccinated dead pet rabbits. They do not currently offer free testing for domestic rabbits unless suspected cases are supplied with a current vaccination certificate. They have never detected the RHDV1 v351 Czech or RHDV1 K5 strain in a reportedly vaccinated rabbit.

Commonwealth Scientific and Industrial Research Organisation (CSIRO) Health and Biosecurity: Undertakes testing for samples submitted through Rabbit Scan as part of the RHDV1 K5 release. All submissions are tested using qRT_PCR to quantify the viral load in samples as well as a strain-specific multiplex PCR assay. Over the last two years the majority of RHDV cases in pet and domestic rabbits has been due to RHDV2. Information on vaccination status of the rabbit samples is patchy. Since the release, no domestic rabbit has tested positive for RHDV1 K5, vaccinated or non-vaccinated. A very large proportion of the total pet rabbit samples submitted were negative for RHDV (possibly cases of myxomatosis). Since the release of K5 in Australia in March 2017, over 500 samples have been tested at this site.

Filavac VHD K+V Vaccine

Submissions made during public consultation for the registration of RHDV1 K5 have asked why New Zealand has not registered the vaccine available in Europe. It has been elucidated by ACVM that the submission made was referring the "Filavac VHD K C+V" manufactured by "Filavac" based in France. This is an inactivated vaccine containing antigen against both RHDV ("classical" strain) and RHDV2, a strain that is exotic to New Zealand. Registration of this vaccine by ACVM has been discussed with wider MPI as an alternative to the registered Cylap RCD vaccine.

Since the RHDV2 strain is not in New Zealand, registration of the vaccine was not deemed warranted and in fact, would interfere with NZ OIE status of being RHDV2 free. It should also be noted that the Cylap vaccine has a good track record for efficacy against RHDV virus in pet rabbits in New Zealand. A search of adverse events reported after use of Cylap RCD vaccine, did not describe any instances of vaccine inefficacy.

Conclusion

Protection of RHDV1 variant vaccines against RHDV1a variants has been demonstrated through the submission of two peer-reviewed journal articles which describe trials where rabbits have been vaccinated with killed vaccines containing RHDV1 antigen and subsequently exposed to RHDV1a virus. As part of this assessment to determine efficacy of the current vaccine against the K5 strain, previous efficacy studies in support of the original Cylap RCD vaccine application were reviewed and accepted as being relevant and supportive of the current application.

Pharmacovigilance reports in both Australia and NZ have been reviewed and do support efficacy of the vaccine against both Czech strain and K5 strain. No reports of inefficacy were found from either country including since the release of K5 in Australia nearly one year ago. Information from experts support efficacy of Cylap RCD given that no vaccinated rabbits have been shown to have died from either the Czech or K5 viral variants and well in excess 500 samples have been tested.

Expert opinion was sought to determine whether duration of immunity of the Cylap RCD vaccine against the K5 strain could be considered similar to duration of immunity against the current Czech strain. This was to ensure that the current on-label dosing regimen would continue be effective at preventing disease in pet rabbits if the K5 strain were to be released in New Zealand.

Expert opinion based on comparison of amino acid sequencing between the strain within the vaccine, K5 and v351, suggests that not only is the Cylap RCD vaccine an appropriate vaccine to induce protection in vaccinated rabbits against disease caused by exposure to K5, but also that the vaccine will give the same duration of immunity for the v351 and K5 strains.

When putting all of the available information together, it is concluded that enough evidence exists to give confidence that the ACVM registered Cylap RCD Vaccine (A007472) will be effective at protecting vaccinated rabbits against the K5 virus were it to be released in New Zealand.

Despite being present in over 20 countries for several decades, currently the only species known to be vulnerable to RHDV1 is the European rabbit (*Oryctolagus cuniculus*). This evidence comes from observations that several other members of the lagomorph family including cottontail rabbits, jack rabbits and hares are not affected.

Testing susceptibility of RHDV1 in non-target animals has been undertaken on a total of 43 separate animal species in countries throughout the world including in China, Europe, Australia and New Zealand. Animal species tested were chosen to ensure

phylogenetic presentation of number of domestic and native species and include the following:

Bush rat, Spinifex hopping mouse, Plains rat, Fat-tailed dunnart, Short-nosed bandicoot, Brush tailed bettong, Tammar wallaby, Brush tailed possum, Koala, Southern hairy-nosed wombat, Short-beaked echidna, Sheep, Cattle, Horse, Goat, Pig, Dog, Cat, Fowl, Ferret, Red fox, Hare, Rat, Mouse, Long-billed corella, Feral pigeon, Silver gull, Brown falcon, Emu, Kiwi, Common blue-tongued lizard, Short tailed bat, Guinea pig, Hamster, Chinchilla and fish, European brown hare, Volcano rabbit, Eastern Cottontail rabbit, Black-tailed Jack Rabbit.

While some species developed antibody titers against RHV+DV, none of the above mention species developed clinical signs of disease. Histological and immunohistological results did not demonstrate any viral genetic material in any of the tissues tested, which suggests the virus cannot survive or replicate in the species tested.

Predators of rabbits have been studied to determine whether exposure to RHDV could result in infection of these species. Oral infection in red foxes and intraocular plus IV infection in dogs has resulted in some animals seroconverting however none have demonstrated signs of disease or viral replication in the studies summarised.

Of note, studies have been undertaken in New Zealand where serum samples were collected from 177 animals including ferrets, feral cats, hedgehogs, hares, and hawks. The animals were resident in areas that had experienced RHDV epidemics 2 months prior to testing. Within each species tested, no hares (34) seroconverted, while 3.3% (1/30) of hedgehogs, 9.8% (5/51) of ferrets, 18% (2/11) of hawks and 43% (22/51) of cats had formed antibodies against the virus. No animals tested showed any clinical signs of RHDV.

In conclusion, many non-target species have been specifically inoculated with RHDV virus over the years and no evidence of infection has been noted. While, seroconversion has been demonstrated in many species, this is merely evidence of exposure and passive immunisation, and not of infection. There have been no reports in any country, including New Zealand, of RHDV1 infection in any species other than the European rabbit since the virus was first reported in 1984. This gives strong support that no non-target animal species will become infected with RHDV1 K5 if it is released in New Zealand.