

REPORT TITLE:

Veterinary Biologics Risk Analysis for the Field Testing and Licensure
of Fort Dodge Animal Health's Rabies Vaccine, Live Raccoon Poxvirus Vector

(Confidential Business Information Deleted Version)

VS Code 1901.R5

June 5, 2007

U.S. Veterinary License No. 112
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I. STATEMENTS OF APPROVAL AND COMPLIANCE

We have reviewed this report and agree that it accurately reflects the updated scientific information: Veterinary Biologics Risk Analysis for the Field Testing and Licensure of Fort Dodge Animal Health's Rabies Vaccine, Live Raccoon Poxvirus Vector, VS Code 1901.R5.

II. SUMMARY

Fort Dodge Animal Health (FDAH) will conduct a field safety study with the experimental Rabies Vaccine, Live Raccoon Poxvirus Vector, VS Code 1901.R5, in accordance with the requirements described in Title 9, Code of Federal Regulations (9 CFR), Part 103.3, and a proposed field safety protocol. Upon the satisfactory completion of this study and all other remaining requirements, FDAH will seek USDA licensure of this product for general distribution and sale. This experimental vaccine must be tested under field conditions and the following risk assessment has been performed to determine if the proposed environmental release of this vaccine entity presents safety risks to animals, public health and the environment.

The safety risk to animals is low. This raccoon poxvirus-vectored rabies vaccine has already been tested to be safe when administered into cats and dogs in one/three year duration of immunity studies. In addition to cats and dogs the vaccine is also safe for mice. The reversion-to-virulence study results indicated that the rRCNV-Rabies is nonpathogenic and can not revert to be virulent.

The safety risk to public health is low. This modified live vector rabies vaccine is neither pathogenic nor replicative, and the Master Seed Virus used for production of this vaccine is avirulent. No reports of human disease are associated with raccoon poxvirus.

The safety risk to the environment is low as well. The results from the reversion-to-virulence study demonstrated that rRCNV-Rabies could not disseminate into body fluids or feces when passed in cats. The potential escape and dispersal of rRCNV-Rabies into the environment is unlikely.

In summary, the overall risk to animals, public health and the environment is low. Therefore, authorization for the licensure, general distribution and sale of the product should be granted due to the little risk of adverse events involved with Rabies Vaccine, Live Raccoon Poxvirus Vector.

III. INTRODUCTION

A. Objective

The objective of this risk analysis is to describe the safety risks, if any, associated with the environmental release of an experimental Category III-Rabies Vaccine, Live Raccoon Poxvirus Vector, VS Code 1901.R5. In this report, the molecular characterization and biological properties of the rRCNV-Rabies construct, and the safety impact of this experimental vaccine on animals, public health and the environment will be discussed. The goal is to provide evidence that this experimental vaccine is safe when administered in cats and dogs under field conditions, and is safe for licensure, general distribution and sale.

B. Proposal

Rabies almost always results in fatal neurological disease in humans and animals, and remains a serious global public health concern (5). FDAH is therefore seeking a global licensure of recombinant rabies vaccine for cats and dogs as an aid in the prevention of rabies virus infection. The final vaccine product will contain live recombinant RCNV vector expressing rabies glycoprotein, [REDACTED] and will be adjuvant-free. The USDA-approved reversion-to-virulence study demonstrated that the rRCNV-Rabies construct is avirulent and nonreplicative in the cats. This experimental vaccine will be administered subcutaneously to healthy cats and dogs at the age of 12 weeks or older.

The proposal is to conduct a field safety test (environmental release) with a Category III-Rabies Vaccine, Live Raccoon Poxvirus Vector, produced by Fort Dodge Animal Health. The studies will be conducted in accordance with the provisions described in 9 CFR 103.3 "Shipment of experimental biological products" and a proposed field safety protocol. The experimental vaccine is to be field tested under normal small animal husbandry practice. Upon satisfactory completion of this study (and other USDA required prelicensing documentation) the vaccine will be eligible for licensure and general distribution and sale.

IV. MOLECULAR CHARACTERIZATION OF THE RECOMBINANT ORGANISM

A. Recipient Characterization:

1. Parental organism:
[REDACTED] raccoon poxvirus [REDACTED]
2. Description of the recipient organism:
Raccoon poxvirus was first isolated from the respiratory tract of raccoons with no clinical symptoms [REDACTED] n

1961-1962 (1, 13, 24). The RCNV is a member of the Poxviridae Family containing a linear and nearly 200 kb double-stranded DNA genome with a hairpin loop at each end. Like other poxviruses (vaccinia virus, fowlpox virus and canarypox virus), RCNV replicates in the cytoplasm and uses its own transcription systems, and has been used as a live vector to express the foreign genes for vaccine development (6, 11, 12, 23).

3. **Genetic modifications used to produce the recipient organism from the parental organism:**

No genetic manipulation was made to the parent strain of RCNV.

4. **Proposed site for Donor DNA insertion:**

Rabies glycoprotein genes [REDACTED], were inserted in the RCNV [REDACTED] respectively.

5. **Identity of the gene(s) located at the insertion site:**

The gene-specific PCRs were used to amplify [REDACTED] gene [REDACTED] inserted at the RCNV [REDACTED], for gene identity testing.

6. **Genetic markers:**

[REDACTED]

B. **Donor Characterization:**

1. **Donor organism(s):**

Rabies virus, a negative-stranded RNA virus, is a member of the genus *Lyssavirus* within the family *Rhabdoviridae*. Rabies virus can infect all warm-blooded animals. Infection with this virus can result in fatal neurological disease. Five structural proteins: the nucleoprotein (N), phosphoprotein (M1), matrix protein (M2), transmembrane glycoprotein (G) and RNA-dependent RNA polymerase (L), are encoded by the 12-kb viral genome (5). It is well known that the viral antigen G protein induces virus neutralizing antibody and protection against lethal rabies virus challenge (2, 6, 11, 12, 19, 23).

2. Donor gene(s):

[REDACTED]

3. **Proposed phenotypic effect of the donor construct(s) in the recombinant organism:**

There was no observable change in the typical cytopathic effect (CPE) compared to RCNV wild type [REDACTED]

[REDACTED]

C. **Construction of the recombinant organism:**

1. **Summary of the construction process:**

[REDACTED]

[REDACTED]

2. Intermediate cloning vector(s):

[REDACTED]

3. Procedure for introducing the genetic modification(s) to the recipient:

[REDACTED]

[REDACTED]

- 4. **Procedure for introducing the genetic modification(s) to the donor genes:**

No modification was made to rabies gene.

- 5. **Screening methods and protocols for the identification and purification of the recombinant organism:**

The recombinant viruses were purified by a standard viral plaque purification technique (6, 7, 11, 12).

[REDACTED]

D. Molecular Characterization of the Master Seed:

- 1. **Master Seed designation:**

The Master Seed of Rabies Vaccine, Live Raccoon Poxvirus Vector,

[REDACTED]

- 2. **Methods and protocols used to establish identification of the Master Seed:**

Identification of the Master Seed was established by the following two methods: a) the gene-specific PCR to examine the physical presence of rabies gene in the RCNV genome and b) IFA to determine expression of rabies protein protein specific monoclonal antibody

- 3. **Purity and safety testing of the Master Seed:**

[REDACTED]

APHIS Form 2008 reports satisfactory results of safety testing in both cats

per the 9 CFR 113.300 and 113.39, and dogs per the 9 CFR 113.300 and

[REDACTED]

- 4. **Extraneous agents testing of the Master Seed:**
The APHIS Form 2008 reports satisfactory results of all extraneous agent testing according to EP 5.2.4.

[REDACTED]

- 5. **Stability of the Master Seed organism at passage levels X and X + 5 (highest passage level):**
The genetic stability of the Master Seed at the passage levels X and X + 5 was determined by PCR testing. No noticeable insertion or deletion occurs within the insertion flanking regions:

[REDACTED]

The phenotypic stability of the Master Seed at the passage levels X and X + 5 was determined by IFA [REDACTED] and blue plaque assay [REDACTED]. No significant difference was observed in rabies protein expression by IFA, and blue plaque assay between passage levels X and X + 5.

The above results indicated that Master Seed of rRCNV-Rabies [REDACTED] was genetically and phenotypically stable under pre-manufacture scale-up procedure to passage 5.

V. BIOLOGICAL PROPERTIES OF THE RECOMBINANT ORGANISM

A. Recipient:

- 1. **Virulence:**
The RCNV appears to be avirulent or naturally attenuated for various domestic and wild animals. Unlike some DNA and RNA viruses, the naked RCNV DNA is not infectious. First, no obvious clinical signs were

observed in the healthy raccoons from which the virus was first isolated (1, 13, 24). Second, safety studies conducted using RCNV wild type revealed no clinical untoward effects with inoculation of RCNV in raccoons, dogs, bobcats, cotton rats, striped skunks, gray foxes, rabbits, domestic cats, American mongooses, sheep, swine, patas (African) and cynomolgus (Asian) monkeys (9, 10). Third, DeMartini *et al.* (4) reported poor antibody response to RCNV-G given orally in sheep, implying that it would be relatively harmless if inadvertently ingested by sheep. Virus transmission between vaccinated and sentinel sheep was not observed or detected serologically. Lastly, Esposito group (8) compared the pathogenicity in experimental animals of RCNV-G/RCNV and vv-G/vv. Results of rabbit skin tests (assessed histopathologically), suckling mouse lethality, and oral infection of monkeys and mice indicated that the RCNV-G was 100- to 1,000-fold less pathogenic than vv-G, 1,000- to 10,000-fold less pathogenic than vv Copenhagen itself, and 100-fold less pathogenic than RCNV itself.

2. Previous use of the recipient organism:

The RCNV has been used as a vector to express feline herpesvirus type 1 genes (21, 22), feline panleukopenia (14, 15), feline parvovirus (15), rabies glycoprotein (11, 12, 14), and *Yersinia pestis* F1 capsular antigen (18). See more details in Section V.A.1.

However, there was only one documented case of human exposure of a recombinant raccoon poxvirus expressing *Yersinia pestis* F1 capsular antigen in a laboratory accident (the disposal needle used to vaccinate animal pricking a female scientist's right index finger). Within 9 days, the patient developed a very small blister that healed within 4 weeks (20).

3. Tissue tropism in susceptible host(s):

The virus was isolated from the upper respiratory tract of raccoon and was reported to localize mainly in the tonsils (1, 13, 24).

4. Horizontal gene transfer/recombination potential:

The potential for horizontal gene transfer/recombination between RCNV and other viruses is unlikely.

5. Host/range specificity:

Serosurveys of natural hosts for this virus other than raccoons have not been conducted. However, the RCNV is rather divergent from other orthopoxviruses. No epidermal vesicles could be demonstrated in various animals by various routes of inoculation with RCNV or RCNV recombinant viruses, suggesting that RCNV may not spread systematically like other orthopoxviruses (4, 8, 9, 10).

6. **Environmental distribution:**

The RCNV was first isolated from upper respiratory tissues of two out of 92 apparently healthy raccoons captured in 1961-1962 during a survey of local wildlife at Aberdeen Proving Grounds, Maryland (1, 13, 24). The current distribution of RCNV in wildlife is unknown.

7. **Geographical distribution:**

The raccoons are widely spread in American (especially in Canada and US) and Asia, and migrated to Europe through Russia from Northeast Asia by hunting or natural migration. The exact geographical distribution of RCNV in raccoons and other wildlife is unknown.

8. **Recommended NIH/CDC Biosafety Levels:**

The Biosafety Level 2 is recommended for handling of the vaccinia virus, however, RCNV is much less pathogenic than vaccinia virus, and RCNV-G construct is 100-fold less pathogenic than RCNV itself (8). The Biosafety Level 1 could be safe enough to handle RCNV-vectored vaccine candidates.

B. **Donor(s):**

1. **Virulence:**

~~_____~~
However, the G genes from the ~~_____~~ are naked DNA, not infectious, and avirulent.

2. **Biological function encoded by the donor gene(s):**

The rabies G, the only protein exposed on the surface of the viral particle, is the mediator of both binding to cellular receptors and entry into host cells. Being a highly immunogenic protein, virus-neutralizing antibodies that are induced against this protein protect animals against rabies infection (2, 6, 12, 14, 19, 23). Furthermore, the rabies G induces cell-mediated immunity (16). It is well known that rabies glycoprotein contributes to protective immunity against lethal rabies virus challenge.

3. **Previous safe use of donor genes:**

Rabies G gene was expressed in *E. coli* (25), vaccinia virus (6), fowlpox virus (23), canarypox virus (23), raccoon poxvirus (12), and even plasmid vector (2). No safety concerns about rabies G gene were reported in these studies.

4. **Tissue tropism in susceptible host(s):**

Neurotropism is the main feature associated with rabies virus infection. Rabies infection initiates in muscle tissue, and then progresses to the

peripheral and central nervous systems. Once virus reaches the brain, it spreads centrifugally to a variety of organs. The spread into the salivary gland, which represents the final phase of the infection, is important for transmission of rabies from animal to animal and from animal to human. Other infected tissues and organs in which rabies can be found include sensory nerve end organs in oral and nasal cavities, taste buds, adrenal glands, pancreas, kidney, heart muscle, brown fat, hair follicles, retina, and cornea (5).

5. **Horizontal gene transfer/recombination potential:**
The potential for horizontal gene transfer/recombination between virulent rabies, rRCNV-Rabies and other viruses is unlikely.
6. **Host/range specificity:**
Rabies virus can infect all warm-blooded animals. The most susceptible species are foxes, coyotes, jackals, bats, and wolves. Dogs, the most frequent vector for transmission to humans, as well as cats and raccoons have been shown to be moderately susceptible to rabies virus infection (5).
7. **Pathogenic or toxic properties of the donor gene(s):**
The rabies gene is nonpathogenic or not toxic.
8. **Ability of the donor genes to produce resistance to therapeutic agents:**
The rabies gene does not produce any known resistance to therapeutic agents.
9. **Recommended NIH/CDC Biosafety Level:**
The Biosafety Level 2 is recommended for handling of the rabies virus.

C. **Master Seed:**

1. **Virulence:**
 - (a) **Target animal:**
See Section IV.D.3 for safety testing of Master Seed rRCNV-Rabies in cats and dogs. In addition, the experimental vaccines were tested in the one-year duration of immunogenicity of rabies vaccine, live raccoon poxvirus vector, in cats and dogs. No local and systemic reactions were observed after cats and dogs were administered subcutaneously a single dose of rRCNV-Rabies vaccine.
 - (b) **Non-Target animals:**
The Master Seed was not virulent in the mice, but has not been directly determined in other non-target animals. Since the Master

Seed is the result of rabies gene insertion into RCNV genome, which further attenuated RCNV. It is unlikely to cause significant, if any, virulence problems in other animals. See more details in Section V.A.1.

2. **Biological effect of the genetic modification at the insertion site(s):**
 - (a) **Biological function encoded by the gene(s) at the insertion site(s):**
Insertion of rabies genes resulted in the disruption of and genes.
 - (b) **Previous safe use of insertion site(s):**
No safety concerns were reported when foreign genes were expressed at insertion site(s). See more details in Section V.A.2.
3. **Purity:**
See Section IV.D.3 for purity testing of the Master Seed rRCNV-Rabies
4. **Genetic stability:**
See Section IV.D.5 for the genetic stability of the Master Seed rRCNV-Rabies, by rabies genes-specific PCR
5. **Phenotypic stability:**
See Section IV.D.5 for the phenotypic stability of the Master Seed rRCNV-Rabies by IFA and blue plaque assay
6. **Tissue tropism in susceptible host(s):**
Tissue tropism in dogs and cats has not been determined directly with this Master Seed. However, no virus was recovered from oral cavity, feces, cervical lymph nodes, liver, spleen or tonsil when high titer of rRCNV-Rabies was inoculated in cats in the reversion-to-virulence study.
7. **Horizontal gene transfer/recombination potential:**
The potential for horizontal gene transfer/recombination between rRCNV-Rabies and other viruses is unlikely.
8. **Shed/Spread capabilities:**
The reversion to virulence (RTV) study results indicated that no spread and shedding was observed in 20 sero-negative cats at 8 weeks of age inoculated orally with rRCNV-Rabies X+3

(The RTV report was approved by USDA on November 7, 2006). A similar study conducted in cats with the parent 7.0 PFU of vKB-JE13 (RCN/rabies G) by different routes (oral, intranasal, conjunctival, or intranasal/ conjunctival) indicated that RCNV is a safe vector (17): (1) no viral shedding was detected (blood, nasal, oral and fecal swabs were negative for RCNV by both virus isolation and by nested-PCR); (2) no horizontal transmission of the virus could be detected (the gang-housed sentinel animals did not develop detectable rabies neutralizing antibodies, and anti-RCN antibodies); and (3) no virus, LacZ expression, and histopathological lesions were detected in a variety of collected tissue samples.

9. **Host/Range specificity:**
The host range specificity of this Master Seed has not been tested. However, the seroconversion was observed in cats, dogs, cattle, horses and pigs.
10. **Effect of overdosing:**
The safety test of immuno vaccine [REDACTED] (10 doses of [REDACTED]) was conducted in the cats and dogs. No clinical signs were observed, and the animals remained well after 7-days observations.
11. **Survivability of the microorganism in the environment:**
The survivability of this organism (Master Seed rRCNV-Rabies [REDACTED]) in the field environment conditions has not been tested yet. However, under the laboratory conditions, the regular dose experimental vaccine [REDACTED] was stored at 2-7°C. The vaccine samples were removed at specified intervals and titrations were performed to determine 27-month real time stability. It was found no significant loss of virus titer when stored at 2-7°C for 27 months ([REDACTED]). This virus is quite stable when stored refrigerated.
12. **Environmental distribution:**
The rRCNV-Rabies [REDACTED] does not exist in the environment. However, the raccoons are widely spread in American, Asia, and Europe.
13. **Recommended NIH/CDC Biosafety Levels:**
The rRCNV-Rabies [REDACTED] is further attenuated by insertion of [REDACTED] rabies [REDACTED] gene into [REDACTED]. Therefore, the rRCNV-Rabies [REDACTED] could be considered as the Biosafety Level 1 organism. See detail in sections V.A.1.& V.A.8.

VI. RISK ASSESSMENT

A. Hazard Identification

Hazard identification consists of identifying all possible adverse events to animal safety, public health safety and environmental safety relative to the field safety testing of Rabies Vaccine, Live Raccoon Poxvirus Vector.

1. Animal Safety

a. Target Species

The rRCNV-Rabies ● immuno vaccines ● were administered subcutaneously in a single dose regimen into the 112 cats and 57 dogs at 12 weeks of age in one/●-year duration of immunity studies, and no adverse reactions were observed post vaccination. The challenge results in one-year DOI studies successfully demonstrated that the above two experimental vaccines meet 9 CFR requirements of efficacy in both cats and dogs. ●

In the reversion-to-virulence study, 20 sero-negative cats at 8 weeks of age were given orally with a titer of ●. No clinical signs were observed, and no virus was recovered from oral cavity, feces, cervical lymph nodes, liver, spleen or tonsil. These results indicate that the rRCNV-Rabies ● is nonpathogenic and nonreplicative in cats.

b. Non-target Species

The rRCNV-Rabies ● immuno vaccines ● were tested in mice (IP route), and no adverse reactions were observed, indicating that the experimental rRCNV-rabies ● vaccine was safe for mice under laboratory conditions.

2. Public Health Safety

a. Summary

The safety of the rRCNV-Rabies ● vaccine has not been assessed in humans directly. Since the rRCNV-Rabies ● is avirulent and non-replicative in the most susceptible target animal-cats. The impact of this rRCNV-Rabies ● vaccine on public health is little.

b. **Probability of Human Exposure**

Human exposure will be limited to the personnel producing the rRCNV-Rabies ● viral stock, vaccine blending and filling, and veterinarian administering the vaccine into the target animals.

c. **Pathogenicity of the Parent Microorganism in Humans**

The rRCNV-Rabies ● is nonpathogenic, and is considered as BSL1 organism.

d. **Virulence of the Vaccine Microorganism in Humans**

The rRCNV-Rabies ● is avirulent.

e. **Possible Outcome of Human Exposure**

The Master Seed rRCNV-Rabies ● has not been assessed in humans directly. However, there are no expected safety concerns associated with human exposure (i.e. handling of vaccine, and handling of vaccinated animals), based on the reversion-to-virulence study in cats and safety studies in dogs and mice. Furthermore, no reports of human diseases are associated with raccoon poxvirus.

3. **Environmental Safety**

There is little impact on environmental safety because rRCNV-Rabies is nonpathogenic and nonreplicative. The potential establishment of rRCNV-Rabies ● in the environment is low although RCNV already exists in nature (for example, raccoon populations).

B. **Release Assessment**

The field safety study of FDAH's Rabies Vaccine, Live Raccoon Poxvirus Vector, VS Code 1901.R5 will be conducted per 9 CFR 103.3 and a proposed field safety study protocol. The study design is summarized below:

1. **Location**

The field safety study will be conducted in 4 or more different states within US, and the exact sites/study investigators will be provided prior to the start of trial.

2. **Characteristics of the Test Sites**

Individual cats and dogs owners/investigators will be recruited to participate in the trial. The animals will be handled under normal small animal husbandry conditions.

3. **Personnel**

Study sponsor

Fort Dodge Animal Health
800 5th Street NW
Fort Dodge, Iowa 50501

Study director

████████████████████
Fort Dodge Animal Health
800 5th Street NW
Fort Dodge, Iowa 50501

Study monitor

████████████████████
Fort Dodge Animal Health
800 5th Street NW
Fort Dodge, Iowa 50501

4. **Experimental Design**

a. **Number of Animals**

Feline: ≥ 600 cats (a minimal of 1/3 cats at 12 weeks of age)

Canine: ≥ 600 dogs (a minimal of 1/3 dogs at 12 weeks of age)

b. **Disposition of Animals**

Described by current small animal husbandry practices at the test sites

c. **Route of Administration**

Subcutaneous route

d. **Dose**

One 1.0 mL-dose

e. **Total Amount of Test Material**

A minimal of 1,200 doses

f. **Frequency and Duration of Exposure**

The single-dose rRCNV-Rabies ● vaccine (any two out of three pre-license serials) will be administered into healthy cats and dogs

at 12 weeks of age or older, and animals will be observed daily for two weeks post-vaccination.

g. Method of Disposing of Waste

By the current small animal husbandry practices at the test sites

h. Decontamination of the Test Site

No decontamination was needed because no virus shedding and spread was observed in the reversion-to-virulence study.

5. Potential for Escape and Dispersion in the Environment

The potential for escape and dispersion in the environment is low because no virus was recovered from oral cavity, feces, cervical lymph nodes, liver, spleen or tonsil when cats were orally inoculated with a high titer [REDACTED] of rRCNV-Rabies in the reversion-to-virulence study.

6. Potential for Establishment in the Environment

It is unlikely for this virus to establish in the environment because of no virus shedding and spread after over dose inoculation.

7. Monitoring

The veterinarian will observe the animals for 30 minutes following vaccination for immediate reactions. After vaccination the animals will be observed daily for two weeks by the owner for any delayed reactions.

8. Contingency Plans in Case of Adverse Event

The study monitor will be notified of any adverse events immediately during the course of the trials. If the risk is deemed significant to other animals, personnel or the environment, individual animals may have to be euthanized. Such events will be reported immediately to the USDA.

C. Risk Characterization

The rRCNV-Rabies is a raccoon poxvirus derived vector vaccine. The raccoon poxvirus Herman strain is avirulent, which was first isolated from healthy raccoons in Maryland. The insertions of glycoprotein genes of challenge [REDACTED] further attenuated the virus.

The reversion-to-virulence study was conducted in the most susceptible target animal, cats. No clinic signs were observed, and no virus was recovered from oral cavity, feces, cervical lymph nodes, liver, spleen or tonsil when cats were inoculated orally with over-dose rRCNV-Rabies [REDACTED] (The RTV report was approved by USDA on November 7, 2006). In addition, the

experimental immuno vaccines were tested in 112 cats and 57 dogs, no adverse reactions were observed post vaccination. It is unlikely that rRCNV-Rabies vaccine has adverse effect on public health and the environment.

Risk characterization for potential to escape and disperse into the environment

1. Likelihood Rating

Likelihood ratings are assigned for animal safety, public health safety and environmental safety, based on the following criteria:

Low = An adverse event is unlikely to occur.

Medium = An adverse event could possibly occur.

High = An adverse event will most probably occur.

The likelihood that the rRCNV-Rabies would escape and disperse into the environment is:

Low = An adverse event is unlikely to occur.

2. Consequence Rating

Consequence ratings are also assigned for animal safety, public health safety and environmental safety, based on the following criteria:

Low = The consequence if the adverse event occurs is not severe (the adverse event is self-limiting and would have negligible impact).

Medium = The consequence if the adverse event occurs is moderately severe (the adverse event will have an impact, but is not permanent and can be treated).

High = The consequence if the adverse event occurs is severe (the adverse event will have an impact, is permanent and cannot be treated).

The consequence rating for the rRCNV-Rabies escaping and dispersing into the environment is:

Low = The consequence if the adverse event is unlikely to occur.

3. Degree of Certainty Rating

Certainty ratings are also assigned for animal safety, public health safety

and environmental safety, based on the following criteria:

- Certain = The rating is supported by direct scientific evidence.
- Moderately Certain = The rating is supported by indirect scientific evidence.
- Uncertain = The rating is not supported by scientific evidence.

The degree of certain rating for the rRCNV-Rabies not having the potential to escape and disperse into the environment is:

- Certain = The rating is supported by direct scientific evidence (17) and [REDACTED]

This is a raccoon poxvirus (avirulent) vector based vaccine, and it is unlikely for rRCNV-Rabies to escape and disperse into the environment.

4. Calculating the Expected Risk for the Potential to Escape and Disperse into the Environment

The expected risk can be calculated for the potential to escape and disperse into the environment based upon the above information. Calculating the Expected Risk in Risk Analysis for Veterinary Biologics (Gay, C. G., Orr, R. L., 1994) the following information is calculated:

- Likelihood Low LL = 1.00
- Consequence Low CL = 1.00

Degree of Certainty Ratings II (Degree of Certainty Ratings I is to be used only if the Likelihood rating is Medium or High and the Consequence rating is Medium or High).

- Certain C = 1.00

Expected Risk = [(likelihood) × (degree of certainty)] × [(consequence) × (degree of certainty)]

$(1.00 \times 1.00) \times (1.00 \times 1.00) = 1.00$

Thus the calculated Expected Risk is 1.00.

5. Risk Rating

The risk rating is determined by referring to Calculating the Expected Risk in Risk Analysis for Veterinary Biologics (Gay, C. G., Orr, R. L., 1994). With an Expected Risk of 1.00, the Risk Rating would be:

Low = Acceptable risk – very little concerns are associated with the rRCNV-Rabies vaccine.

Risk characterization for the potential to become established in the environment

1. Likelihood Rating

Likelihood ratings are assigned for animal safety, public health safety and environmental safety, based on the following criteria:

Low = An adverse event is unlikely to occur.

Medium = An adverse event could possibly occur.

High = An adverse event will most probably occur.

The likelihood that the rRCNV-Rabies would become established in the environment is:

Low = An adverse event is unlikely to occur.

It is unlikely for rRCNV-Rabies to establish in the environment because no virus shedding and spread were observed in the most susceptible target animal, cats.

2. Consequence Rating

Consequence ratings are also assigned for animal safety, public health safety and environmental safety, based on the following criteria:

Low = The consequence if the adverse event occurs is not severe (the adverse event is self-limiting and would have negligible impact).

Medium = The consequence if the adverse event occurs is moderately severe (the adverse event will have an impact, but is not permanent and can be treated).

High = The consequence if the adverse event occurs is severe (the adverse event will have an impact, is permanent and cannot be treated).

The consequence rating for the rRCNV-Rabies becoming established in the environment is:

Low = The consequence if the adverse event occurs is not severe (the adverse event is self-limiting and would have negligible impact).

The RCNV vector is avirulent, and insert genes are not toxic. The rRCNV-Rabies is nonpathogenic, and this vaccine will be limited to the target animals. No adverse impact is expected.

3. Degree of Certainty Rating

Certainty ratings are also assigned for animal safety, public health safety and environmental safety, based on the following criteria:

Certain = The rating is supported by direct scientific evidence.

Moderately Certain = The rating is supported by indirect scientific evidence.

Uncertain = The rating is not supported by scientific evidence.

The degree of certain rating for the rRCNV-Rabies vaccine not having a potential to become established in the environment is:

Certain = The rating is supported by direct scientific evidence.

The rRCNV-Rabies is nonpathogenic and it lacks the capability to replicate if it escapes into the environment. In addition, duration-of-immunity studies and reversion-to-virulence study by Fort Dodge Animal Health confirmed the safety of the Rabies Vaccine, Live Raccoon Poxvirus Vector.

4. Calculating the Expected Risk for the Potential to Become Established in the Environment

The expected risk can be calculated for the potential to become established in the environment based upon the above information. Calculating the Expected Risk in Risk Analysis for Veterinary Biologics (Gay, C. G., Ott,

R. L., 1994) the following information is calculated:

Likelihood Low LL = 1.00
Consequence Low CL = 1.00

Degree of Certainty Ratings II (Degree of Certainty Ratings I is to be used only if the Likelihood rating is Medium or High and the Consequence rating is Medium or High).

Certain C = 1.00

Expected Risk = [(likelihood) × (degree of certainty)] × [(consequence) × (degree of certainty)]

$$(1.00 \times 1.00) \times (1.00 \times 1.00) = 1.00$$

Thus the calculated Expected Risk is 1.00.

5. Risk Rating

The risk rating is determined by referring to Calculating the Expected Risk in Risk Analysis for Veterinary Biologics (Gay, C. G., Orr, R. L., 1994). With an Expected Risk of 1.00, the Risk Rating would be:

Low = Acceptable risk – very little concerns are associated with the Rabies Vaccine, Live Raccoon Poxvirus Vector

VII. RISK MANAGEMENT AND COMMUNICATION

A. Procedure

Risk management uses the information from the above-described sections to determine means of reducing or eliminating safety risks to animals, public health or the environment.

B. Environmental Release

The safety risks of the Rabies Vaccine, Live Raccoon Poxvirus Vector to animals, public health and the environment are low. A risk rating of low is acceptable, with very little concerns associated with the proposal to conduct the requested Field Trial and the subsequent licensure of Fort Dodge Animal Health's Rabies Vaccine, Live Raccoon Poxvirus Vector.

C. Risk Communication

The overall risk of rRCNV-Rabies vaccine to animals, public health and the

environment is low (Finding of No Significant Impact-FONSI). Therefore, FDAH requests publication in Federal Register announcing availability of an environmental assessment and Confidential Business Information (CBI)-deleted risk analysis as soon as APHIS/CVB approves this risk analysis.

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