Rabies Vaccine, 
Live Adenovirus Vector (AdRG1.3 baits), Trade Name: ONRAB – Environmental Assessment

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Prepared and revised by:
Canadian Centre for Veterinary Biologics
Terrestrial Animal Health Division
Canadian Food Inspection Agency

The information in this environmental assessment was current at the time of its preparation. It is possible that the situation may have changed since that time. Please consult the Canadian Centre for Veterinary Biologics, if you have any questions.

1. Introduction

The oral rabies vaccine is manufactured by a private company, Artemis Technologies Inc. (ATI), which is proceeding with the licensing of this product. Most of the proposed sites for the use of this product are areas in which skunk or fox infection with the arctic fox strain of rabies virus has been detected in recent years, and which were normally included in the baiting zone for the licensed "ERA" wildlife rabies vaccine (an attenuated strain of rabies virus). Although ERA baits work well in immunizing foxes against rabies, they do not have efficacy in skunks, thus allowing skunks to maintain the risk of rabies infection for the fox population. In addition to data supporting ONRAB’s efficacy in skunks, field research conducted since 2006 has indicated that this product may also be effective in immunizing raccoons at risk of being infected with the raccoon strain of rabies. The distribution of several million baits in Canada since 2006 did not result in any serious human contact or public safety issues, and there have been encouraging results in the assessment of field efficacy in skunks and raccoons. This public document contains information on the vaccine, target animal and non-target animal safety, human safety and environmental considerations regarding this human adenovirus-vectored rabies vaccine for this field use in Canada.

2. Vaccine

Artemis Technologies Inc. proposes to license the Rabies Vaccine, Live Adenovirus Vector, in Canada for use in wildlife.

This live, human adenovirus-vectored rabies vaccine virus could cause infection in humans who accidentally break open the bait packages, if the person is not already immune. Human adenovirus type 5 is ubiquitous, and usually causes only a mild, self-limiting respiratory disease in children under the age of five. There is also no association with allergic or toxic effects with the wild-type virus, and studies in weanling mice have indicated that the vaccine virus is not likely to be any more pathogenic than the wild-type virus. An infection caused by the vaccine virus could be symptomatic in immunocompromised children or adults, but the probability of this exposure to virus via these wildlife rabies baits is small. No infection of wildlife species in the area intended for distribution of this bait is expected, since human adenovirus does not replicate in most animal species. Replication of human adenoviruses has been reported in cotton rats, but this species is normally found in the southern United States, and no clinical disease is reported following infection of this species.
3. Molecular and Biological Characterization of Parental and Recombinant Organism

The proposed vaccine qualifies as a Class II Veterinary Biologic (vaccine using a live vector to carry a recombinant-derived foreign gene). More details on the regulation of veterinary biologics produced by biotechnology can be found in Veterinary Biologics Guideline 3.2, available on the website of the Canadian Food Inspection Agency (CFIA) website. This vaccine construct is a human adenovirus-vectored recombinant vaccine containing a gene sequence from the ERA strain of wildlife rabies vaccine virus, inserted into the E-3 region of the human adenovirus type 5. The licensed vaccinia-vectored recombinant rabies vaccine (VR-G) contains the same ERA rabies virus glycoprotein sequence. The master seed, also referred to as "AdRG1.3," was re-plaqued on suitable cell types to produce the viral master seed, which was tested for purity, identity and genetic stability by the CFIA's Biologics Evaluation Laboratory (BEL), and the viral master seed and master cell stock have been approved for use in veterinary vaccine production in Canada.

The potential for in vivo recombination of the human adenovirus-vectored recombinant vaccine virus with field and other vaccine viruses is unknown, but it is considered small. For intergenic recombination to occur, two related viruses would have to infect the same cell. The likelihood of co-infection of individual cells would be predicted to be a rare event because the proposed vaccine has a single viral component and the vaccine virus does not lead to infection in the target species or other wildlife species that are likely to consume the baits. Therefore, occurrence of recombination in vivo is not expected.

4. Animal Safety

This experimental rabies vaccine, live adenovirus vector, was found to be safe in experimental studies in skunks (intended target species) as well as in several non-target species. A variety of animal species has been included in the safety studies on AdRG1.3, including horses, pigs, sheep, dogs, cats, chickens, meadow voles, deer mice, foxes, cotton rats, squirrels, rabbits, groundhogs, and cows. No adverse reactions in the animals studied were found following oral inoculation of the experimental vaccine, while in most cases antibodies against the rabies viral protein were detected on day 28 post-exposure. Although all the animals were deemed to be clinically normal after oral inoculation of AdRG1.3, viral nucleic acids were detected in some tissues or the feces of some vaccinated animals, suggesting that AdRG1.3 was replicating or persisting in these hosts for a few days to a couple of weeks post-vaccination. Replication of adenovirus in immunocompromised animals such as nude mice or SCID mice did not appear to result in adverse reactions, but these animals failed to produce neutralizing antibodies against rabies due to their inherent immune deficiency. Collectively, these results indicate that AdRG1.3 may retain some replication capability in both healthy and immunocompromised animals, but it does not cause adverse reactions (toxicity) in these animals.

Studies showed that the Master Seed Virus is genetically and phenotypically stable up to passage MSV+10, and is free of extraneous agents. All of the studies in target and non-target species indicate that the host range and tropism of the rabies vaccine, live adenovirus vector, were not altered from the parent human adenovirus type 5 strain.

In the rare circumstance that food animals are observed consuming the wildlife rabies baits, the usual withdrawal time of 21 days for veterinary biologics, prior to slaughter of the animal, applies. Tetracycline may be added as a marker in the outer bait matrix. As such, milk from any lactating dairy animals observed consuming the vaccine baits should be withheld for five days to prevent any antibiotic residues from contaminating the milk. We recommend that intact baits observed in pastures or on agricultural products such as beans or lettuce be relocated to better wildlife habitat, and that any produce actually contaminated with the liquid vaccine from broken baits be discarded.

5. Human Safety

Hazards to public health and safety are not expected. Two incidents of inadvertent human contact with ERA wildlife rabies baits were documented by the Ontario Ministry of Natural Resources (OMNR) in 2005. The first case involved a six-year-old. The child with an open wound on the finger removed a partially chewed bait from a dog's mouth. It was undetermined as to whether the attenuated ERA rabies vaccine came in contact with the child's open wound, but as a precaution, the child was treated with post-exposure rabies
vaccination. The second incident involved a 16-month-old who stuck a bait in his mouth; however, it was determined that the blister-pack did not break and there was no significant contact with the vaccine. ERA has been used to immunize wild foxes in Ontario since 1989. Over 14 million ERA baits were aerially distributed between 1989 and 2004, and there have been reports of only two other significant human contacts, which were treated with post-exposure rabies vaccination as a precaution. The probability of human exposure to the experimental vaccine baits for wildlife remains low, given the same annual coverage areas for aerial distribution of AdRG1.3. The proposed AdRG1.3 expressing the rabies glycoprotein should be even safer than ERA, due to its inability to induce rhabies.

Most vaccinated animals do not significantly shed the vaccine virus for more than a day or two. Infection of people with human adenovirus type 5, more frequent in children under five years old, is not generally associated with serious illness. However, adenoviruses are among the many pathogens and opportunistic agents that can cause serious infection in congenitally immunocompromised persons, in patients undergoing immunosuppressive treatment for organ and tissue transplants and for cancers, and in patients infected with human immunodeficiency virus (HIV). In addition, adenovirus infection is observed to be more severe in children than adults. Therefore, the AdRG1.3 virus could present health hazards to humans, especially children or immunocompromised adults, given that AdRG1.3 is a live virus with replication potential. Each bait has a label that includes the telephone number for public information. A communication plan is in place for these experimental baits and for other wildlife rabies baits used in Canada. It includes the recommendation that people with significant exposure to any of these live wildlife rabies vaccines seek medical advice.

6. Environmental Consequences

The vaccine virus is stable at room temperature for days to weeks, but OMNR has studied the disappearance of other wildlife rabies vaccines from baited areas, and reports that most baits are eaten within two weeks of distribution in rural areas. The limited host range of human adenovirus reduces the risk of spread in target and non-target wildlife or domestic animals. The risk of release of this experimental rabies vaccine is not expected to be greater than that for the other licensed rabies vaccines (ERA, VR-G), and it is actually considered to have fewer potential adverse consequences.

The potential for accidental human exposure is low, since the wildlife baits are typically distributed in rural areas away from houses. The widespread immunity in humans over the age of five for related human type 5 adenoviruses would make person-to-person spread of infection unlikely, even if significant contact with the blister pack contents of a bait were to occur. Personnel experienced in the distribution of wildlife rabies vaccines will be conducting the distribution, and will adhere to all the usual precautions taken when distributing these baits.

7. Monitoring and Record Keeping

The conditions of use will be documented by the CCVB in a Permit to Release Veterinary Biologics prior to the start of the vaccine distribution. This permit will specify the conditions for release of these experimental baits, and will stipulate requirements for immediately stopping the distribution and informing the CCVB if any significant adverse events attributable to the vaccine are observed.

The monitoring of the distribution will consist of maintaining the records associated with the delivery of the baits and with recorded public concerns.

8. Consultation and Contacts

Manufacturer
Artemis Technologies Inc.
51 Watson Road South
Guelph, Ontario N1L 1E3

9. Recommendation

A Permit to Release Veterinary Biologics may be issued to provincial authorities responsible for wildlife rabies control to allow distribution of Rabies Vaccine, Live Adenovirus Vector, CCVB File no. 900VV/R5.0/A22 (unlicensed).
10. References


