EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Specific aspects with oral vaccines to be used in dogs and various species

Towards Rabies Elimination in Asia-Pacific
- From Theory to Practice

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Specific aspects

The finished product (the vaccine) is presented as bait for oral suspension containing a live, attenuated rabies vaccine strain as active substance

- ✓ The bait comprises attractant for the target species for which the vaccine is intended (not to non-target species)
- ✓ The bait casing protects the vaccine virus
- ✓ The bait may contain a biomarker (topical or systemic)
- ✓ The vaccine suspension is inside a bait filled in a blister

Unique method of administration

- ✓ Vaccine is released in the habitat of target species - further testing to mimic environmental conditions is needed (baiting system – ecology)
- ✓ Mass vaccination - a proven tool for rabies prevention

Centralised marketing authorisation

In the EU, vaccines against rabies used in oral vaccination need to have marketing authorisation and be monitored continuously to ensure their quality, safety and efficacy

Pre-authorisation	Regulatory mechanism to support development/research and to promote innovation for the benefit of public and animal health
Scientific evaluation	•Risk assessment to evaluate oral vaccines and distribution factors •Basis for marketing authorisation (valid throughout the EU) •To ensure that the benefits outweigh the risks
Monitoring Supervision	•Continuous monitoring and supervision medicines that have been authorised in the EU, across their lifecycle , to ensure that their benefits outweigh their risks. •Guidance
Information	•Scientific assessment reports and relevant information public available

Oral vaccines used

Vaccine strains selected based on safety and efficacy profiles

- ✓ Requirements and guidance; both for the target species and non-target species including humans that might be in contact with baits or a recently vaccinated animal

Live attenuated virus vaccines

- ✓ Used for wildlife and free-roaming dogs
- ✓ Safety concerns: residual pathogenicity in rodents, vaccine-associated rabies cases in target (foxes) and non-target species (cow)
- ✓ Genetic diversity of variants within certain commercial vaccine strains - presence of a mix different variants has been shown

Recombinant GMO vaccines

- ✓ Used for wildlife, cats and dogs

Oral vaccines used in Europe

All oral vaccines used in Europe are modified live attenuated virus GMO vaccines based on the Street Alabama Dufferin (SAD) strain isolated from a naturally infected dog in 1935

Several vaccines have been used since 1980s, the attenuated vaccine strains SAD Bern and SAD B19 were the most widely used

Centrally authorised oral vaccines;

- ✓ Rabigen SAG2 oral suspension for red foxes and raccoon dogs (2000)
- ✓ Rabitec strain SPBN GASGAS, oral suspension for foxes and raccoon dogs (2017)
- ✓ Both vaccines are intended for use by competent authorities only, within the framework of national rabies eradication programmes

Oral candidate vaccines for dogs

- ✓ Modified live attenuated virus vaccine (SAD Bern, SAD B19)
- ✓ Modified live attenuated virus GMO vaccine (SAG2, rERAG333E)
- ✓ Modified live attenuated recombinant vector vaccines
  - vaccinia virus vector (V-RG vaccinia rabies glycoprotein)
  - human adenovirus vector (AdRG1.3)
  - canine adenovirus vector (CAV-2-E3Δ-RGP)
  - orf virus (ORFV) vector
  - rabies virus vector (RV SN10-333 etc.)
- ✓ These vaccines are frequently used off-label

Quality aspects

Stability of the vaccine during production, storage, transport and use (release titre, minimum titre on the label)

Vaccine virus

- ✓ Genetic characterisation of the vaccine strain
- ✓ Genetic markers to discriminate the vaccine strain from other rabies virus
- ✓ Stability of the genetic marker (mice test)
- ✓ Stability

Bait casing

- ✓ Adapted to the target species
- ✓ Palatable, easy ingestion
- ✓ Physical stability
- ✓ Thermal stability (climatic settings)
- ✓ Mechanical stability
- ✓ Biomarker stability

Blister

- ✓ The suitability and integrity
- ✓ Labelling

Safety aspects

Safe for the target species and for major endemic the non-target species (e.g common local rodents/ carnivores) likely to be attracted by the baits

- More stringent for dogs than for wildlife (association with human/puppies); testing in non-human primates
- The most sensitive age (juvenile animals)
- The least attenuated passage level, the maximum titre
- 10 times the maximum virus titre likely to be contained in 1 vaccine bait
- Repeat administration of 1 dose
- Observation period (daily)
- Clinical signs and the presence of rabies virus in the brain using reference diagnostic tests
- Pregnant animals and lactation, immuno-compromised animals

Safety aspects

- ✓ Spread of the vaccine strain

  In natural and experimental conditions; freshly vaccinated dogs

- ✓ Dissemination in the vaccinated animal (excretions, saliva)

  For dogs absence of the virus should be demonstrated 4-7 days post-immunisation

- ✓ The absence of reversion or increase in virulence

  Stability of the genetic marker

- ✓ Biological properties of the vaccine strain
- ✓ Recombination between rabies or other lyssaviruses
- ✓ Field studies

Human safety

In case a person comes into contact with the vaccine it is most probably by skin contact and should be of no consequence, however as it is a live rabies virus vaccine

- ✓ Public warning on the blister and on the bait (a warning pictogram with a text)
- ✓ Product information, package leaflet
  - Handle the baits with care
  - Recommended to wear disposable rubber gloves when handling and distributing baits
  - Proposed first aid measures (WHO recommendation)
- ✓ Public awareness

Environmental safety

Ecotoxicity - the potential harmful effects of the product for the environment and any necessary precautionary measures to reduce such risks

Hazard identification

- Safety for a range of target and non-target species (adverse events)
- Human safety, children, immuno-compromised people, humans cohabitate (human-dog bond, saliva)
- The potential of transmission to non-target species (cats)
- The shedding potential of vaccine virus in direct contact (saliva)
- The capacity of vaccine virus to survive, establish and disseminate in the environment
- The vaccine’s excipients (biomarker)
- The risk of pollution of the environment - in case not all baits are consumed (non-biodegradable blister)
- For products containing or consisting of GMO (in the EU: Directive 2001/18/EC)

Efficacy aspects

- ✓ The intake of one single vaccine - sufficient to ensure active immunisation to prevent infection by rabies virus
- ✓ A target species adapted vaccine strain should be used
- ✓ Efficacy of the oral vaccine shall be demonstrated in each species for which the vaccine use is claimed
  - Species specific vaccine; clear differences have been observed in vaccine titres needed to induce a protective immune response against rabies after oral vaccination in different reservoir species
- ✓ The protection status cannot be checked by serology only; a virulent challenge is necessary

Efficacy aspects

- ✓ Minimum age (at least 3 months of age without rabies specific antibodies)
  - The influence of passively acquired and maternal derived antibodies on the efficacy of a vaccine
- ✓ The quantity of vaccine, the minimum virus titre and the most attenuated passage level
- ✓ Relevant challenge strain
  - different from the one used in the production of the vaccine
- ✓ Challenge-dose finding studies to determine the dose and route that is sufficient to induce clinical signs of rabies in at least 80-90% of unvaccinated control animals for each target species

Efficacy aspects

- ✓ The number of animals (without antibodies)
  - sufficient to obtain statistically significant and clinically reliable results (25 animals)
- ✓ Immunisation route; oral route of administration
- ✓ Immunogenicity (in terms of DOI) by challenge
  - the interval between vaccination and challenge (at least 180 days)
  - long lasting immunity: protective immunity for 1 year
  - Observation after challenge (90 days)
    - control animals signs of rabies and the presence of rabies virus in the brain (80%)
    - vaccinated animals no show signs of rabies (statistically equivalent number)
- ✓ OOI by seroconversion (a part of efficacy assessment)

Efficacy aspects

Species specific vaccine:

- ✓ Clear differences have been observed in vaccine titres needed to induce a protective immune response against rabies after oral vaccination in different reservoir species

Field studies

- ✓ In the EU, the MUMS policy allows the omission of efficacy field trials when sufficiently justified (following the outcome of the scientific advice)
  - Provided that the laboratory data are fully supportive of vaccine's efficacy, the collection of data from the field could be handled as a follow-up measure
  - The vaccine will be used under governmental supervision
  - Neither OIE nor WHO require any efficacy proof for a rabies wildlife product in the field, prior to granting the marketing authorisation

Follow-up: Periodic safety update reports (PSURs)

- ✓ A worldwide safety experience of the vaccine
- ✓ At defined time points succinct summary information together with a critical scientific evaluation of the benefit-risk balance of the vaccine in the light of new or changing post-authorisation safety information
  - evidence of safety concerns
  - adverse events
  - lack of efficacy
  - environmental issues
- ✓ Further investigations on a specific issue or actions to protect animal and public health

Requirements and Guidance for oral vaccines

EU. Directive 2001/82/EC and GLs; VICH GL41 Target animal safety: examination of live veterinary vaccines in target animals for absence of reversion to virulence; Environmental risk assessment for immunological veterinary medicinal products" (EMA/CVMP/074/95) GMO Directive 2001/18/EC

EDQM. European Pharmacopoeia monographs, monograph for rabies vaccine (live, oral) for foxes and raccoon dogs (746/2013)

OIE. Chapter on rabies and manual of diagnostic tests and vaccines for terrestrial animals (2018)

WHO. Guidance and reports on oral vaccination of dogs against rabies

Any questions?

Further information

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