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Guideline on data requirements for veterinary medicinal products for the prevention of transmission of vector-borne diseases in dogs and cats

Draft

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Table of contents

Executive summary

This guideline provides recommendations for the design and conduct of studies to support the efficacy of veterinary medicinal products (VMPs) intended for the prevention of transmission of vector-borne pathogens (VBPs) in dogs and cats, which can be transferred by blood-feeding arthropods. The guideline outlines the requirements for laboratory and field studies.

Prevention of transmission of vector-borne disease in the context of this guideline means the reduction of the risk of transmission of VBPs by killing or repellent effect against the vector prior to the transmission of the VBPs. This guideline, therefore, establishes criteria for the demonstration of efficacy of a VMP in order to be granted a claim for the reduction of the risk of transmission of VBPs.

1. Introduction (background)

Vectors are living organisms, usually arthropods such as dipterans, fleas, lice, mites and ticks, that can transmit pathogenic (micro)organisms from one infected host to another non-infected host (human or animal), causing disease. Vector borne diseases (VBDs) are caused by a wide range of infectious agents including viruses, bacteria and parasites (protozoa and helminths).

Given the zoonotic potential of some VBDs, there are 'One Health' considerations for the management of ectoparasitic infestations in dogs and cats for protecting public health in addition to the health and well-being of companion animals (Day, 2011; Mencke, 2013).

Veterinary medicinal products may provide indirect protection against VBPs by repelling or killing the vector.

Across the EU, many ectoparasiticides are authorised as VMPs for the treatment of tick and flea infestations in dogs and cats. The efficacy of these VMPs was assessed in accordance with the 'Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats' (EMEA/CVMP/EWP/005/2000). Similarly ectoparasiticides authorised as VMPs for the treatment of lice, mites and diptera have been assessed against the efficacy thresholds set in the guideline 'Demonstration of efficacy of ectoparasiticides' (7AE17a, 1994). However, those guidelines do not give advice on how to design studies for the demonstration of efficacy in the reduction of the risk of transmission of VBPs.

The repellent, insecticidal and/or acaricidal efficacy of a VMP demonstrated against a vector may not be directly linked to the efficacy of the VMP in reducing the risk of VBDs. That is, a VMP that has achieved the required threshold for efficacy sufficient for an insecticidal and/or acaricidal claim may not be effective at reducing the risk of transmission of a VBP, as the vector may still have the ability to transmit the pathogen causing the VBD before it is killed.

2. Scope

This guideline provides guidance on how to support an indication for a VMP for the reduction of the risk of transmission of canine and feline VBPs transferred by blood-feeding arthropods.

This guideline applies to all applications where, according to Directive 2001/82/EC, new data has to be generated to support clinical efficacy. Immunological VMPs and biocides are excluded from the scope of this guideline.

3. Legal basis

This document should be read in conjunction with Directive 2001/82/EC. Applicants should also refer to relevant European and VICH guidelines, including those listed among the references at the end of this document.

In accordance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes and Directive 2010/63/EC on the protection of animals used for scientific purposes, the 3R principles (replacement, reduction and refinement) should be applied whenever possible.

4. General consideration

For VMPs with insecticidal/acaricidal and/or repellent properties, a claim for the reduction of the risk of transmission of VBPs needs to be demonstrated by laboratory and/or clinical field studies (irrespective of the method of administration).

The underlying principle for the reduction of the risk is the killing and/or repellent effect against the vector prior to the transmission of the VBP. In principle, the following aspects should be considered:

- Unless otherwise justified, it is expected that efficacy of the VMP against the defined vector(s) will have been confirmed according to the requirements of existing guidelines (Vol. 7AE17a, 1994 and EMEA/CVMP/EWP/005/2000-Rev. 3). This implies that the mode of action and the dosing regimen against the vector (repellent and/or killing effect, duration of persistent effect) are known.
- An already authorised VMP with a new claim for the reduction of the risk of vector-borne disease transmission should usually have the same dosing regimen as already authorised for the acaricidal/insecticidal/repellent effect of the product. In case a change in the dosing regimen (increased treatment frequency or dose) is necessary for this new claim, new tolerance and dose justification study/ies should be provided.
- Unless otherwise justified, the efficacy of a VMP for the reduction of the risk of transmission of VBPs has to be proven by appropriate clinical studies under laboratory and field conditions.
- Efficacy should be confirmed for each VBP transmission, extrapolation from one VBP species to another is not acceptable.
- Clinical studies, whether laboratory trials or field studies, should be conducted according to VICH GL9 Good Clinical Practices (GCP) or GLP.

Appropriate statistical methods in line with the CVMP guideline on statistical principles for veterinary clinical trials (EMEA/EWP/81976/2010) should be applied in all clinical studies. It should be noted that lower infection rates of the vectors might require higher numbers of study animals.

To evaluate the suitability of a claim on reduction of the risk of transmission of VBPs, the speed of kill/repellent effect of the VMP against the ectoparasites from the dog or cat in relation to the transmission time of a VBP from the vector to host is considered to be supportive information.

4.1. General study design

The reduction of the risk of transmission of canine and feline VBPs should be demonstrated under defined conditions and performed with the final formulation for marketing administered at the proposed dose and dosage interval confirmed to be effective against the vector (except the situation

where a change in dosing regimen is considered necessary; please see above). When designing a clinical study the following aspects should be taken into consideration to ensure that the study will provide conclusive information:

- The mode of transmission of a given VBP by its respective vector;
- The minimum time period of feeding by the infesting vector required for the transmission of the specific VBP, if available;
- The time period from the transmission of a VBP until the presence of detectable infection parameters (e.g. clinical signs, serological, antigen or DNA detection) in the final host animal, for confirmation of the infection/disease in the host;
- Epidemiological considerations (e.g. the prevalence rate for the VBP in the vector population, zoonotic potential);
- Appropriate method(s) to determine the infection/infectivity status of the vector should be applied;
- Appropriate diagnostic method(s) to determine the infection/disease in the final host animal and, if necessary, confirmatory methods should be applied.

The evaluation of the claimed effect should be based on the absence/presence of the VBP in the final host animal, the antibody response of the final host animal, and/or the molecular detection of specific DNA of the VBP in the final host animal (with or without clinical signs of the disease), as appropriate for each VBP. The type of evaluation conducted may vary depending on the study design and the availability of appropriately validated diagnostic procedures. The applicant should justify the diagnostic approach used to demonstrate transmission after challenge or natural infection. With respect to the claimed VBP, it is considered important to select appropriate time points for efficacy evaluation taking into account current knowledge on diagnostic options and the biology of the disease.

5. Laboratory trials

5.1. Type of study

Unless otherwise justified, at least one well-designed study under laboratory conditions covering the entire period of reduction of the risk of disease transmission is considered necessary for each claimed VBP. Studies should be performed in a parallel group design with a treated (test) group and an untreated or placebo-treated group (negative control group). The inclusion of a negative control group is considered necessary in order to confirm the validity of the test system. A rescue protocol needs to be defined for all animals that have become infected.

5.2. Study animals

The experimental animals should be clinically healthy and proven to be free of infections with the targeted VBPs (e.g. immunologically naive, proven as sero- and/or PCR-negative). Methods confirming the presence/absence of VBP/VBD in the animals before and after challenge should be justified and validated with a sufficient diagnostic accuracy.

Included animals should not have been treated with an ectoparasitic substance within a time frame that might impact on the study outcome. Whenever indicated (e.g. for ticks), animals should be tested for their ability to carry adequate numbers of parasites prior to the start of the study. This pre-allocation infestation should be done with uninfected vectors. The origin, sex, age, body weight and

type of hair coat of animals should be described. The housing conditions and group allocation should follow the 'Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats' (EMEA/CVMP/EWP/005/2000 Rev.3).

5.3. Treatment

The VMP should be administered to the study animals of the test group before the first infestation with the vector at an appropriate time point for preventing VBP transmission, i.e. when an adequate level of efficacy is expected to have been reached (repellent/insecticidal/acaricidal) after product administration. The appropriate time point may vary depending on the mode of action of the active substance, and the pharmaceutical form (e.g. collar, spot-on solution).

The chosen treatment dose should preferably be the established minimum recommended treatment dose (or a dose as close as possible to the minimum recommended dose).

5.4. Information on the vector

Laboratory studies may be performed either with laboratory-bred vector strains artificially infected with a VBP or with vectors from infested habitats with a known prevalence of the VBP. The origin and number of the vector(s) chosen for these studies should be described and justified. Methods used to induce infections in the vector should be described in the study reports, taking into account their reproducibility and validity.

For characterisation of the vector, the following parameters should be considered:

- Classical taxonomic determination, including data on the geographic origin of the particular batch of used vectors;
- Molecular barcoding or similar relevant data confirming the species classification.

5.5. Information on the vector borne pathogen

The VBP used in experiments should be properly characterised, and the following data should be provided:

- The biology of the VBP in the vector and in the host;
- Classical taxonomic determination including the data of the geographic origin;
- Molecular barcoding or similar relevant data confirming the species classification; such as DNA sequences deposited in GenBank or similar depository.

The infection rate of the batch of vectors used for each challenge should be confirmed and justified depending on the VBP. The number of vectors analysed to estimate the proportion of the batch infected, the method to confirm the infectivity and all results should be reported and justified.

5.6. Procedure of infestation

A description of the infestation method of the study animals (both treated and untreated) with the vector should be provided. The information should include the number of vectors per animal and the time points for the initial and repeated challenges reflecting the period of the effect claimed (e.g. short term up to 4 weeks, long term effect more than 4 weeks). For a VMP with short-term effect, it is recommended to perform two challenges, one at the start and one close to the end of the claimed

protection period, while for a VMP with long-term effect, multiple challenges are required. In such case, the time points of re-challenge should be justified. The number of challenges during the course of the study should be kept as low as possible for animal welfare reasons without compromising the integrity of the study. The experimental model should be robust enough to reflect field conditions in terms of number of challenges, duration of the challenge, number of bites (exposures) in the field, infection rate of the vector, climatic conditions, etc.

The vector should be left on or near the host animals for a time period which is known to ensure the transmission of a VBP. The time point for removal of the vectors should be indicated. During the study period, a defined number of untreated control animals, which have been infested with the vector at the same time as the animals in the test group, should become infected with selected pathogen(s). Appropriate measures should be applied to reduce any negative impact on animal welfare (e.g. appropriate exit clauses and rescue protocols; see 5.1).

5.7. Evaluation of efficacy

The primary efficacy parameter should be the relative blocking efficacy of the test product on VBP transmission. Possible secondary criteria should also be defined. A definition of success (non-infected host animals, which are free of infections with the targeted VBPs; e.g. immunologically naive, proven as sero- and/or PCR-negative) and failure (infected host animals, in which the presence of VBP has been confirmed) should be provided.

The difference in the proportions of infected animals in the treatment group and in the untreated control group must be statistically significant.

Depending on the study design, there are several possible approaches for calculating the blocking efficacy. The efficacy threshold should be ≥90%.

The recorded efficacy should be presented together with its confidence interval.

The following example is a common approach:

Calculation of the blocking efficacy based on infective vector challenges

This approach is independent of the number of animals in the study groups and calculates the percentage of protection in comparison to the number of consecutive pre-infection challenges.

$$\text{Protection}\,(\%) = 100 \times \frac{\text{IcC} - \text{IcT}}{\text{IcC}}$$

Where

- IcC = the “infection proportion” calculated as the number of infected animals in the untreated control group divided by the total number of pre-infection challenges with vectors from a batch infected with the pathogen in the ***untreated control group***
- IcT = the “infection proportion” calculated as the number of infected animals in the treatment group divided by the total number of pre-infection challenges with vectors from a batch infected with the pathogen in the ***treatment group***.

6. Field trials

Unless otherwise justified, field trials should be conducted and may constitute pivotal data where no valid laboratory transmission model is available. The trials should be conducted with naturally infected vectors/animals, and should be randomised, blinded and controlled.

The studies should be conducted in Europe in different geographical locations. The applicant should provide information on the seasonal prevalence rate for the VBP in the vector population, considering the seasonal occurrence of the vector parasites, ecological conditions and lifestyle/husbandry of target animals (see also 6.1).

6.1. Information on study animals

Only animals tested negative for both the VBP and the relevant immune response should be considered for efficacy evaluation. Animals that, at study enrolment, tested positive for the VBP of concern should be excluded from efficacy evaluation for that specific VBP. The detection methods used should preferably be based on generally acknowledged procedures combining direct and indirect diagnostic tools, e.g. pathogen detection (e.g. by PCR, culture or staining like immunofluorescence) or antibody detection.

6.2. Infestation and evaluation of infestation level

Under field conditions, the animals will be exposed to naturally infected vectors. Before the first expected exposure of the enrolled animals to the vectors, the product should be administered at an appropriate time point for preventing VBP transmission, i.e. when an adequate level of efficacy is expected to be reached after product administration.

The chosen treatment dose should preferably be the established minimum recommended treatment dose (or a dose as close as possible to the minimum recommended dose) and the established dosing interval.

When the efficacy of blocking the transmission of a VBP by a vector is intended to be demonstrated under field conditions, a control group (positive or negative) should be included. In those cases where laboratory data are not fully supportive of prevention of transmission, the inclusion of an untreated (negative) control group in the field study is considered necessary, to obtain information on the real transmission pressure. An adequate number of initially VBP-free animals in the untreated control group should be diagnosed positive for a VBP infection compared to the treated animals to ensure the validity of the study. A rescue protocol needs to be defined for all animals that have become infected.

6.3. Evaluation of efficacy

Under field conditions, it is recommended to calculate the efficacy by comparing the incidence of infection of the VBD in the treated and the control group. The time period should be appropriate, and the lifecycle and prevalence of the vector (e.g. a year, a season or a month) should be taken into consideration.

A) The reduction of the risk of VBPs transmission (%) for a defined time period calculated as follows:

$$\text{The reduction of the risk of VBPs transmission (\%)} = \frac{\text{incidience in the control group} - \text{incidience in the treated group}}{\text{incidence in the control group}} \times 100$$

The incidence (%) should be calculated for each group as follows:

$$\frac{\text{no. of newcases of infected animals}}{\text{no. of negative animals initially enrolled} - \text{no. of lost or dead animals}} \times 100$$

B) To overcome problems with dogs lost to follow-up during field studies (e.g. death, withdrawal, etc.), and to account for potential differences in time spans during which the animals were included in the study; the incidence density rate (IDR) could be used.

The IDR is defined as the number of newly infected cases per population at risk during a given follow-up time period calculated in animal-time. IDR is calculated by dividing the number of new cases by the number of animal-time as follows:

$$\text{IDR (per 100 cases per time)} = \frac{\text{number of new cases}}{\text{animal – time (years)}} \times 100$$

"Animal-time" is the sum of the periods of observation for each animal during which the animal is free from the disease (i.e. is at risk). As soon as an animal becomes diseased, it no longer contributes to this value. Usually IDR is expressed in years but the IDR can also be calculated on a monthly basis.

Animals that were tested only once at D+0 after which they were excluded then from the study (e.g. lost, dead), do not contribute at any time to the incidence calculation.

$$\text{Protection (\%)} = 100 \times \frac{\text{IDRc} - \text{IDRt}}{\text{IDRc}}$$

IDRc = the IDR in the control group

IDRt = the IDR in the treated group.

Concerning the methods of efficacy evaluation, the reduction of the risk of VBPs transmission % should be ≥90%. The recorded efficacy should be presented together with its confidence interval.

The proportions of infected animals between the treatment and negative control group must differ statistically significantly. For positively controlled field studies, non-inferiority or superiority to an authorised veterinary medicinal product with recognised efficacy in the indication concerned should be demonstrated.

7. Summary of product characteristics (SPC)

The SPC draft should take into account the guidance in the Notice to Applicants (Volume 6C).

Section 4.2 (Indications for use)

This section should list the specific name of the VBDs against which the product has demonstrated sufficient efficacy (effective against VBP transmission), as confirmed in the documentation of part 4, e.g.

"*Reduction of the risk of infection with <name of VBP> via transmission by <name of vector> for up to <time period reflecting the proposed recommended treatment interval for efficacy against the pathogen transmission>. The effect is indirect due to product's activity against the vector.*"; or "*By [repelling and/or killing] the vector [name of the vector], the product reduces the risk of transmission of the VBP [name of the pathogen]*".

Section 4.4 (Special warnings for use)

A warning for the animal owner should be included that the risk of VBP transmission cannot be completed excluded, e.g. by using the following example:
"After treatment <an attachment of single ticks> <feeding of single insect (fleas, phlebotomus etc.)> cannot be excluded (for locally acting products) or a transmission of infectious diseases cannot be completely excluded since the <arthropod> <insect> has to attach to the host before achieving the ectoparasiticidal effect (for systemically acting products)."

Section 4.5 (Special precautions for use)

In context with data on the onset of effect or with the extrapolation from data on the speed of kill, the following warning for owner should be included if necessary:

"The protection may be insufficient the <first hours/ days> after administration of the product."

Section 5.1 (Pharmacodynamic properties)

Relevant information about the clinical trial(s) might be included in this section. However, if relevant, appropriate information should be mentioned in section 4.4 or 4.5, as appropriate.

Definitions

Vectors: Vectors are living organisms that can transmit disease-causing organisms; that is, they can transmit VBPs from an infected host to an uninfected host.

Vector-borne diseases (VBD): Vector-borne diseases are diseases caused by pathogens that are transmitted by a vector. The vector may merely be a passive carrier of the infectious agent, but many kinds of infectious agents undergo a stage of biological development in the vector, known as biological vectors. In this case, both the vector and the host are essential for the multiplication and life cycle of the infectious agent.

Vector-borne pathogens (VBP): Vector-borne pathogens are disease-causing organisms that are transmitted between their hosts by arthropod vectors. Vector-borne pathogen transmission occurs when host, vector and pathogen interact in space and time within a permissive environment.

Pre-infection challenge: For each animal the number of consecutive challenges with an infected vector population until the transmission of a pathogen has been diagnosed.

Incidence density rate: The number of new cases of an infection at risk in a given follow-up time period calculated in animal-time.

References

CVMP Guideline on the demonstration of efficacy of ectoparasiticides; Vol. 7AE17a, 1994.

CVMP Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats (EMEA/CVMP/EWP/005/2000-Rev 3).

CVMP Note for Guidance on fixed combination products (EMEA/CVMP/83804/05)

CVMP Guideline on the conduct of pharmacokinetic studies in target animal species (EMEA/CVMP/133/99)

CVMP Guideline on statistical principles for veterinary clinical trials (CVMP/EWP/81976/2010)

Day, MJ (2011). One health: the importance of companion animal vector-borne diseases. Parasit Vectors 4, 49.

Directive 2001/82/EC of the European Parliament and of the Council as amended on the Community code relating to veterinary medicinal products.

Directive 2010/63/EC of the European Parliament and of the Council as amended on the protection of animals used for scientific purposes.

Good Laboratory Practice (GLP) (Council Directive 88/320/EEC)

Mencke, N (2013): Future challenges for parasitology: vector control and 'One health' in Europe: the veterinary medicinal view on CVBDs such as tick borreliosis, rickettsiosis and canine leishmaniosis. Vet Parasitol 195, 256-271.

Question and answer on the CVMP guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005)

VICH Guideline 9 (GL9) on Good Clinical Practice (CVMP/VICH/595/1998)