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Guideline on data requirements for veterinary medicinal products intended to reduce the risk of transmission of vector-borne pathogens in dogs and cats

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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 reduction of the risk 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 pre-clinical studies and clinical trials.

1. Introduction (background)

Vectors addressed in this guideline are living organisms, usually blood-feeding arthropods such as dipterans, fleas, lice, mites and ticks, that can transmit pathogenic (micro)organisms from an infected host to a non-infected host (human or animal), which can lead to 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 before transmission of pathogens occurs. This may be achieved if the VMP is characterised by a sufficiently fast killing activity or repellency against blood-feeding vectors such that preventing or interrupting feeding occurs before transmission of VBPs.

Across the EU, many ectoparasiticides are authorised as VMPs for the treatment of tick and flea infestations in dogs and cats. Since 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) came into effect, the efficacy of such products was assessed in accordance with this guideline. Similarly, ectoparasiticides authorised as VMPs for the treatment of lice, mites and dipterans have been assessed against the efficacy thresholds set in the guideline 'Demonstration of efficacy of ectoparasiticides' (7AE17a, 1994). However, these guidelines do not give advice on how to design pre-clinical studies and clinical trials to demonstrate efficacy in reducing the risk of transmission of VBPs.

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

2. Scope

This guideline provides guidance on the efficacy requirements for VMPs intended 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 Regulation (EU) 2019/6, new data have to be generated to support the efficacy. Immunological VMPs and biocides are excluded from the scope of this guideline.

3. Legal basis

This document should be read in conjunction with Regulation (EU) 2019/6. Applicants should also refer to relevant CVMP 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

In principle, 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 pre-clinical studies and clinical trials (irrespective of the route of administration and pharmaceutical form).

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

- It is generally expected that the efficacy of the VMP against the defined vector(s) will have been confirmed according to the requirements of existing guidelines (7AE17a, 1994 and EMEA/CVMP/EWP/005/2000). This implies that the mode of action and the dosing regimen against the vector (repellent and/or killing effect, speed of kill, duration of persistent effect) are known.
- An already authorised VMP with a new claim for the reduction of the risk of transmission of a VBP should generally 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 duration of treatment, frequency or dose) is necessary for this new claim, new tolerance and dose justification study/ies should be provided.
- The efficacy of a VMP for the reduction of the risk of transmission of VBPs has to be proven. It is recommended to demonstrate the efficacy by appropriate pre-clinical studies and clinical trials under laboratory and field conditions. Nevertheless, the omission of a type of study (laboratory or field conditions) could be accepted if appropriately justified, and where the provided data are sufficiently robust to demonstrate efficacy.
- Efficacy should be confirmed for each VBP, extrapolation from one VBP species to another is not acceptable.
- Although extrapolation from one vector species to another vector species is theoretically possible, such extrapolation would need to be justified by means of robust scientific data.
- Pre-clinical efficacy studies should follow the requirements for Good Clinical Practice (GCP) and/or Good Laboratory Practice (GLP), as appropriate (depending on the nature of the studies). In case GCP and/or GLP is not applied (e.g. absence of certified GLP status), traceability, accuracy, integrity and correctness of data should be ensured, and the use of such data in pivotal studies should be justified.

  Clinical trials shall be conducted in accordance with established principles of GCP. Deviations shall be justified.

- To evaluate the suitability of a claim for the 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 important information, but not sufficient to justify such claims by itself.

4.1. General study design

The reduction of the risk of transmission of canine and feline VBPs should be demonstrated under conditions representative of the field conditions. The final formulation of the product should be administered at the recommended dose and dosage interval confirmed to be effective against the vector (except in the situation where a change in dosing regimen is considered necessary; please see above). When designing a pre-clinical study or a clinical trial, 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 tests, antigen or molecular detection-based assay for confirmation of infection (specific DNA)) 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 efficacy parameters that have been defined in the study protocol, e.g. 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.

Confidence intervals around the calculated efficacy (see sections 5.7 and 6.3) should be presented for completeness; it is not intended to compare their lower bounds to a minimum efficacy threshold.

For all studies involving the use of animals, utmost care must be given to the welfare of any animals used and all procedures must be approved by regulatory authorities and an animal ethics committee (EMA/CHMP/CVMP/JEG-3Rs/450091/2012).

5. Pre-clinical studies

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 study results. 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, absence of haematological evidence of VBPs). Methods confirming the presence/absence of VBP/VBD in 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. 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/length of hair coat of animals should be described. 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).

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 to reduce the risk of VBP transmission so that an adequate level of efficacy is expected to have been reached (repellent/insecticidal/acaricidal) at the time of infestation. 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, tablet).

The treatment dose is generally expected to be the same as the dose recommended for the antiparasitic effect, but for the studies the established minimum recommended treatment dose should be used.

5.4. Information on the vector

Pre-clinical 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 vectors should be adequately infected to ensure transmission of the VBP. The origin and number of the vector(s) chosen for these studies should be described and justified. The 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;

- Relevant data to confirm the species classification (e.g. molecular barcoding).

5.5. Information on the vector-borne pathogen

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

- The biology of the VBP in the vector and in the host (e.g. route of transmission, feeding behaviour of the vector (including duration of feeding), pathogen transmission rates and time, migration paths and incubation time of pathogens in their vectors);
- Classical taxonomic determination, including data on the geographic origin;
- Relevant data to confirm the species classification (e.g. molecular barcoding).

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. It should be noted that lower infection rates of the vectors might require higher numbers of vectors or study animals.

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 effect up to 4 weeks, long-term effect more than 4 weeks). For a VMP with short-term effect, it is appropriate 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 a 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. In exceptional and well-justified circumstances, e.g. in case the submission of field data is not possible, the experimental model should be designed to reflect field conditions in terms of challenges, duration of the challenge, number of bites (exposure) 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 the selected pathogen(s). Appropriate measures should be applied to reduce any negative impact on animal welfare (e.g. appropriate withdrawal criteria and rescue protocols; see 5.1 and 5.2).

5.7. Evaluation of efficacy

The primary efficacy parameter should be the relative risk reduction in the treatment group with respect to the control group 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, absence of haematological evidence of VBPs) 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 should be statistically significant.

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

The following example is a common approach:

Calculation of 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.

$$\text{Efficacy } (\%) = 100 \text{ x } \frac{\text{IcC} - \text{IcT}}{\text{IcC}}$$

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. Clinical trials

Unless otherwise justified, at least one clinical trial should be conducted. Clinical trials may also constitute pivotal data where no valid laboratory transmission model is available. Clinical trials should be conducted with naturally infected vectors/animals, and should be randomised, blinded and controlled. Appropriate statistical methods in line with the CVMP 'Guideline on statistical principles for clinical trials for veterinary medicinal products (pharmaceuticals)' (EMA/CVMP/EWP/81976/2010) should be applied in all clinical trials.

Clinical trials should be multi-centred and conducted in Europe in different geographical locations where the studied VBP is known to be endemic. In case this is not feasible, an appropriate justification should be provided. Whenever possible, 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.

6.1. Information on study animals

Only animals tested negative for both the VBP and relevant immune response against the VBP should be considered for efficacy evaluation. When more than one VBP is being assessed, animals that, at study enrolment, tested positive for one of the VBPs of concern should be excluded from the efficacy evaluation for that specific VBP. The detection method(s) 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 and thus baseline prevalence data (primarily in the target animal) should be generated prior to the study initiation.

Baseline data should be representative of the whole study area. Before the first expected exposure of the enrolled animals to the vectors, the product should be administered at an appropriate time point to reduce the risk of VBP transmission so that an adequate level of efficacy against the vector, depending upon the vector and/or the mode of action (insecticidal/acaricidal/repellent), is expected to have been reached at the time of infestation.

Clinical trials involve privately owned pets; the VMP should be used according to label recommendations. 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 should be used.

When the efficacy in reducing the risk of 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 reduction of the risk of transmission, to obtain information on the real transmission pressure, the inclusion of an untreated (negative) control group in the clinical trial should be considered while having regard to animal welfare concerns. In case of animal welfare concerns, untreated control animals can be withdrawn from the study if necessary by way of a rescue protocol. An adequate number of initially VBP-free animals in the untreated control group should be diagnosed positive for VBP infection compared to 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

For negatively controlled clinical trials

Under field conditions, it is recommended to calculate the efficacy by comparing the incidence of infection in the treated and the untreated (negative) 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 is calculated as follows:

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

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

$$\text{Incidence (\%)} = \frac{\text{number of new cases of infected animals}}{\text{number of negative animals initially enrolled} - \text{number of lost or dead animals (unrelated to the VBD)}} \text{x } 100$$

B) To overcome problems with animals lost to follow-up during clinical trials (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:

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

"Animal-time" is the sum of the periods of observation for each animal during which the animal is free from the disease but still exposed to it (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 daily, weekly or monthly basis, depending on the context of the study and the disease.

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

$$\text{The reduction of the risk of VBPs transmission } (\%) = 100 \text{ x } \frac{\text{IDRc} - \text{IDRt}}{\text{IDRc}}$$

Where:

- IDRc = the IDR in the control group;
- IDRt = the IDR in the treated group.

The reduction of the risk of VBPs transmission % should be ≥90%. The proportions of infected animals between the treatment and negative control group should differ statistically significantly.

For positively controlled clinical trials

Non-inferiority to an authorised veterinary medicinal product that has been approved for the indication against VBP transmission being claimed should be demonstrated where such a product is available. An appropriate non-inferiority margin should be based on statistical reasoning and on clinical judgement, and should be tailored specifically to the particular clinical context.

The incidence of the vector infection during the trial should be reported to ensure the internal validity of a positively controlled trial.

7. Summary of product characteristics (SPC)

Section 3.2 (Indications for use for each target species)

This section should list the specific name of the VBP(s) against which the product has demonstrated sufficient efficacy (effective in the reduction of the risk of 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 <time period reflecting the proposed recommended treatment interval for efficacy against pathogen transmission>. The effect is indirect due to the product's activity against the vector."*

or

"By <repelling> <and/or> <killing> the vector <name of the vector>, the veterinary medicinal product reduces the risk of transmission of the vector-borne pathogen <name of the pathogen>".

Section 3.5 (Special precautions for use)

Special precautions for safe use in the target species

A warning for the animal owner should be included that the risk of VBP transmission cannot be completely excluded, e.g. by using the following example:

"After treatment <an attachment of single ticks> <feeding of single insect (fleas, phlebotomus etc.)> cannot be completely excluded. Transmission of infectious diseases cannot be completely excluded since the <arthropod> <insect> has to attach to the host before achieving the ectoparasiticidal effect."

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

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

Section 4.2 (Pharmacodynamics)

Relevant information about the clinical trial(s) might be included in this section. However, if relevant, appropriate information should be mentioned in SPC section 3.4 or 3.5, as appropriate.

Definitions

Vectors: Vectors are living organisms (usually blood-feeding arthropods) 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 (mechanical vector) 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 in the population at risk in a given follow-up time period calculated in animal-time.

Rescue protocol: A protocol established to protect animals from harm, such as but not restricted to having clear-cut withdrawal criteria, intensive monitoring and rescue medications.

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