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Guideline for the evaluation of efficacy of ectoparasiticides - general requirements

Draft

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This guideline replaces the 'Guideline for demonstration of efficacy of ectoparasiticides' (7AE17a).

Comments should be provided using this template. The completed comments form should be sent to vet-guidelines@ema.europa.eu.

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Executive summary

This guideline provides general guidance on the data requirements, the design and conduct of pre-clinical studies and clinical trials to support efficacy for an ectoparasiticidal veterinary medicinal product. Appropriate methods and approaches to demonstrate efficacy against the target ectoparasites are presented and important aspects to consider when designing and conducting studies, including consideration of the 3Rs principles are outlined. Given the range of ectoparasites encountered in veterinary medicine and the differences in their clinical consequences for animals and risks (including zoonoses) posed to humans, higher levels of efficacy may be needed against certain ectoparasites. More detailed and specific guidance is available in species-specific guidelines.

1. Introduction (background)

This guideline replaces guidance document 7AE17a entitled 'Demonstration of Efficacy of Ectoparasiticides' which was first published in 1994 and aims to provide general guidance on the evaluation of efficacy of ectoparasiticides containing novel or established active ingredients.

This updated guideline takes into consideration the experiences gained in the assessment of data submitted in support of applications for ectoparasiticidal veterinary medicinal products since the previous guideline was published. It takes account of current scientific knowledge and regulatory practices and, in particular, data requirements set out in Annex II of Regulation (EU) 2019/6.

The terminology used in this updated guideline when describing ectoparasiticidal effects has been adapted to be consistent with Regulation (EU) 2019/6. Thresholds for demonstrating efficacy have been reviewed to ensure consistency with CVMP species-specific guidelines on efficacy requirements for ectoparasiticidal products. For the purpose of this guideline, resistance to ectoparasiticides means the selection of a specific heritable trait (or traits) in an ectoparasite population as a result of exposure of that population to an active substance, resulting in a significant increase in the percentage of the population that will survive to a standard dose of that chemical when used as recommended (CVMP Reflection paper on resistance in ectoparasites (EMA/CVMP/EWP/310225/2014)).

In addition, the 3Rs principles (replacement, reduction and refinement) have been taken into account when providing guidance on the design and conduct of efficacy studies.

Given the need to reduce the risk of antiparasitic resistance developing, measures to reduce such risks should be considered when designing and conducting pre-clinical efficacy studies and clinical trials (see section 8.3). The efficacy of the proposed dose should be demonstrated in appropriate dose confirmation studies prior to the conduct of clinical trials under field conditions (see sections 5 and 6).

Guidance relevant for the demonstration of efficacy for combination products that include at least one active substance with an ectoparasiticidal effect as well as clarifications on the general approach to the demonstration of efficacy of generic/hybrid ectoparasiticidal veterinary medicinal products are also included.

As it is desirable that a consistent approach to the wording of indications for comparable products is followed and in order to ensure the efficacy profile that has been demonstrated for the concerned products and their correct use is clear for the prescriber and user, a number of recommendations for appropriate wording of indications is provided. In addition, recommendations are included on the evaluation of the onset of efficacy and the duration of efficacy for the prevention of re-infestations, where needed, to ensure appropriate use.

2. Scope

This guideline is intended to provide general guidance on the demonstration of efficacy of ectoparasiticidal veterinary medicinal products.

All ectoparasiticidal veterinary medicinal products, irrespective of their route of administration, and intended to treat or prevent infestations with ectoparasites, whatever their mode of action or the target species, are considered to fall within the scope of this guideline. This includes both locally acting and systemically acting products. Although veterinary medicinal products with a repellent or growth inhibitory effect (Insect Growth Regulators) are not strictly speaking ectoparasiticidal, the general principles set out in this guidance may also be applied to those products. However, this guideline does not give guidance on how to demonstrate efficacy for the prevention of transmission of vector-borne pathogens, as separate guidance is available on that aspect.

The principles set out in this guideline describe the general approach to demonstrating efficacy of ectoparasiticidal veterinary medicinal products against all arthropod species that depend upon a host animal to complete their lifecycle i.e., where at least one parasitic stage occurs on the animal or requires feeding on the animal. However, these principles can also be applied to veterinary medicinal products targeting insects such as nuisance or biting flies given that similar methods are used for demonstrating efficacy against those parasites.

3. Legal basis

The guideline should be read in conjunction with the data requirements set out in Regulation (EU) 2019/6 and, in particular, Annex II of that Regulation.

Ectoparasites are arthropods (invertebrates with a chitinous exoskeleton) that live outside the body of their host. Article 4(13) of Regulation (EU) 2019/6 defines 'antiparasitic' as a substance that kills or interrupts the development of parasites, used for the purpose of treating or preventing an infection, infestation or disease caused or transmitted by parasites, including substances with repelling activity.

Consequently, this guideline is applicable to products that have antiparasitic properties (as defined above) against ectoparasites and should be read in conjunction with related CVMP species-specific guidelines which provide more detailed guidance and information and with other relevant guidelines such as:

- CVMP Guideline on specific efficacy requirements for ectoparasiticides in cattle (EMA/CVMP/625/2003);
- CVMP Guideline on specific efficacy requirements for ectoparasiticides in sheep (EMA/CVMP/411/2001);
- 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) (including the Q&A document on that guideline, EMA/CVMP/EWP/82829/2009);
- CVMP Guideline on data requirements for veterinary medicinal products intended to reduce the risk of transmission of vector-borne pathogens in dogs and cats (EMA/CVMP/EWP/278031/2015);
- CVMP Reflection paper on resistance in ectoparasites (EMA/CVMP/EWP/310225/2014).

All animal experiments should be conducted taking into account section I.1.7 of Annex II of Regulation (EU) 2019/6 and the 3Rs principles (replacement, reduction and refinement), notwithstanding the place of conduct of the experiments. Alternatives to *in vivo* test methods should be employed whenever possible.

4. General requirements

The aim of treatment with an ectoparasiticidal veterinary medicine is to eliminate or reduce the number of arthropod parasites or protect animals from them, in order to maintain animal health.

Studies for each ectoparasite species and each stage of the life cycle against which efficacy is claimed should be provided. The applicant should justify the type of studies (*in vitro* and *in vivo* pre-clinical studies and clinical trials) for each parasite species and stage.

In order to demonstrate the efficacy of an ectoparasitic product, the following stepwise approach supported by pre-clinical and clinical data is recommended:

- characterisation of the pharmacological activity, including pharmacodynamic effects, pharmacokinetic properties and the mode of action,
- information concerning development of resistance and related risk in animals,
- dose determination, including dose interval, duration of treatment and any re-treatment interval(s),
- dose confirmation, including immediate and persistent efficacy testing, as appropriate,
- clinical trial(s).

In principle, pre-clinical studies should establish the required dose and dosing interval of the active substance(s) against the intended target parasite(s) and clinical trials should confirm under field conditions the results of the pre-clinical studies.

It is recommended that pre-clinical efficacy studies (including dose determination and dose confirmation studies) 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 carried out taking due account of the VICH Guidelines on Good Clinical Practice (GCP).

Where relevant and depending upon the route of administration and site of effect (local or systemic), the influence of climatic conditions such as ambient temperature and rainfall on the efficacy of the product should be evaluated. Where applicable, the influence of water temperature on efficacy of the product should be evaluated (e.g. veterinary medicinal products intended for use in finfish).

It may be the case that resistance in certain ectoparasites varies between geographical locations. If that is the case, such variation in resistance to the test substance should be taken into account when investigating efficacy and selecting the location of clinical trials. Efficacy should in principle be tested in susceptible ectoparasites. In situations where there is a significant risk that study animals harbour resistant parasites, the susceptibility of the field isolates should be tested, so that efficacy results can be appropriately interpreted. The number of studies and extent of the data required will usually be dependent upon the results of preliminary *in vitro* studies investigating antiparasitic effects of the active substance(s) against the target ectoparasite(s) and the potential spectrum of activity and the dose and duration of exposure required to achieve the desired effect.

5. Pre-clinical studies

5.1. Pharmacological activity and mode of action

The pharmacodynamic effect of the active substance(s) on the target ectoparasite(s) should be adequately described in terms of the exposure required (amount and duration), speed of onset and duration of effect. The mode of action of the active substance(s) (repellent, killing, anti-feeding, growth regulating etc.) and the life-cycle stage(s) of an ectoparasite against which an antiparasitic effect is intended (ova, larva, adult etc.) should be described and supported by appropriate data. Approximate effective concentrations which may be derived from *in vitro* studies should be identified and may be used as a basis to investigate possible dose rates.

For those products with a systemic mechanism of action or where systemic absorption of the active substance(s) of a locally-applied product is expected, the pharmacokinetic profile of the active substance(s) in the target animal species should be described. In such cases, pharmacokinetic data should be used to support the selection of an appropriate dosage regimen and/or support extrapolation of efficacy data between different formulations or routes of administration.

5.2. Dose determination studies

The purpose of dose determination studies is to establish the effective dose, dosing interval, treatment duration and any re-treatment interval(s) to ensure an adequate level of efficacy against the targeted ectoparasite(s). Preferably, the final formulation should be used. Where justified, a non-final formulation may be used in investigational studies. In such cases, the relevance of the findings from studies conducted with a non-final formulation would need to be justified.

The ectoparasite species and their stage(s) of life cycle used in dose determination studies should be appropriately selected to ensure their relevance for the proposed indications for the product. Naturally infested (by transmission through close contact with infested animals) or, where feasible, artificially infested animals can be used.

Ideally, four groups, each consisting of a sufficient number of animals to allow appropriate statistical analysis, should be administered 0.5, 1 and 2 times the anticipated recommended dose, with one group untreated or administered placebo/vehicle. Unless there are specific welfare concerns associated with infestation by the target ectoparasite(s), an untreated control group should be included and delayed treatment of the untreated control group should be considered once sufficient time has lapsed to allow comparison between a treated and an untreated group.

Each group should harbour or be uniformly infested with adequate numbers of each species of ectoparasites. Single or mixed infestation may be used; however, having regard to the 3Rs principles and to reduce the number of studies and therefore study animals, it is recommended to investigate mixed infestations where possible for products targeting more than one ectoparasite, providing the individual ectoparasites can be suitably differentiated and the welfare of study animals is not compromised.

Study animals in each of the dose groups should be managed under similar experimental conditions and husbandry practices should be described. Appropriate welfare of study animals should be ensured.

The route and method of administration should be the same as that proposed in the application. The timing and number of ectoparasite counts should be justified, considering the biology of the ectoparasite(s) and the anticipated duration of treatment effect and any treatment interval(s).

In principle, dose determination studies should be conducted for each target animal species and for each species of the intended target ectoparasites. However, in keeping with the 3Rs principles and in order to minimise the number of studies and study animals, applicants may consider identifying the least susceptible species of target ectoparasite(s) (preferably by means of *in vitro* laboratory susceptibility data supported by *in vivo* data if the *in vitro* method has been validated and results are correlated with *in vivo* efficacy data) and focus dose determination studies on the least susceptible ectoparasite(s).

For products intended for topical use without systemic action (i.e. exhibiting a repellent or killing effect), *in vitro* tests investigating effective doses and/or concentrations against the proposed target ectoparasites may be utilised in support of the selection of a suitable range of doses or concentrations of the active substance.

In order to ensure acceptability of findings from dose determination studies, it is recommended that:

- the formulation used is the final (or near final) formulation or has been demonstrated to be equivalent to the formulation intended for marketing,
- the product is applied according to the proposed method and route of administration,
- adequate infestation of target ectoparasite species has been established,
- the number of study animals is adequate,
- approach to identification and counting (including timing of counting) of ectoparasites is appropriately justified.
- The difference in counts between treated and untreated animals must be statistically significant at a level of 5% ($p \leq 0.05$).

5.3. Dose confirmation studies

At least two dose confirmation studies are recommended to demonstrate the efficacy of a new product against each of the proposed ectoparasite species and stage(s) of development. Further details on the design of such studies are provided in section 6 below.

Where applicable, at least one study using naturally infested animals is required. In order to adequately reflect differences in husbandry practices and climatic conditions, unless otherwise justified, dose confirmation studies should be performed in different geographical and climatic regions.

Where laboratory isolates are used to artificially infest study animals, it is recommended to use laboratory isolates that have been genetically enriched from more recent field isolates (about every 6 years) and ensure that laboratory isolates are sufficiently representative of current field isolates in the EU in terms of vigour of infestation and resistance profile. For animal welfare reasons, ectoparasites used should be free of vector-borne pathogens (e.g. transmission of the cestode *Dipylidium caninum* by *Ctenocephalides felis* fleas).

In order to ensure acceptability of findings from dose confirmation studies, it is recommended that:

- the formulation used is the final formulation intended for marketing, or has been demonstrated to be equivalent to the formulation intended for marketing,
- the recommended dose and method of administration is used,
- statistically adequate numbers of treated and control animals are included and justification for treatment group sizes is provided,

- approach to identification and counting (including timing of counting) of ectoparasites is appropriately justified.

When efficacy is to be investigated for parasites in which strains resistant to another substance have emerged and the product is likely to be used in animals exposed to resistant strains, a controlled trial that includes animals exposed to resistant strains of the target ectoparasite(s) will be necessary to demonstrate adequate efficacy, if the new active substance has:

- a similar mode of action to that of the existing ectoparasiticide against which resistance has developed,
- a close chemical analogy to that of the existing ectoparasiticide.

6. Clinical trials

6.1. General principles

Clinical trials are intended to examine under field conditions the efficacy and safety of the product under normal conditions of animal husbandry or as part of normal veterinary practice. The design and conduct of clinical trials should take into account the principles of replacement, reduction and refinement and should also ensure appropriate animal welfare in terms of avoiding causing pain, suffering or distress to study animals by the procedures used in the clinical trials.

Clinical trials should be conducted in at least two different geographic and climatic regions, which can be considered representative of the European Union. This approach is recommended to ensure that the findings reported are suitably representative of the target species, husbandry practices, environmental/climatic conditions and possible variations in susceptibility in the region(s) where the product is intended for use. The prevalence of the target ectoparasite species must be described. The final formulation intended for marketing should be used at the recommended dose and route. Any deviation should be justified by the applicant.

6.2. Design and conduct

The design and conduct of clinical trials should take into account guidance available in the CVMP Guideline on statistical principles for clinical trials for veterinary medicinal products (EMA/CVMP/EWP/81976/2010). Data from a sufficient number of treated and control animals exposed to adequate infestation(s) with the target ectoparasite(s) are required. Untreated control groups should be used provided there are no serious welfare implications of the disease. Where an untreated control group is not justified because of animal welfare reasons, a positive control using an established product may be included. When a non-inferiority evaluation is planned it should be ensured that the infestation rate is large enough in the test and the positive control group to obtain sufficient assay sensitivity.

In exceptional cases, where scientifically and clinically justified, studies may be performed without the use of control animals (e.g. in the case of animals infected with *Sarcoptes scabiei*).

Where applicable, groups of treated and control animals should be established by randomisation to groups. Ectoparasite-related conditions and/or diseases in study animals should be described before initiation of treatment and any change in clinical symptoms and/or diseases should be monitored during the study period and reported. A statistical analysis of the results of each clinical trial to evaluate the overall efficacy of the product should be conducted for each arthropod species against which efficacy is claimed. As clinical trials should evaluate both efficacy and target animal safety, study animals should be observed and clinically examined at appropriate intervals during and after

treatment, to evaluate safety of the veterinary medicinal product. All adverse events should be recorded.

7. Demonstration of efficacy

The efficacy of the product should be evaluated using appropriately controlled tests. The guidance included in this section is applicable to both pre-clinical studies and clinical trials, as appropriate.

Efficacy should be determined by identifying and counting of ectoparasites on the animal, or, where this is not possible, by estimation. The choice of sampling times should be justified and take account of any seasonal or daily effect on maximum infestation levels, and predilection sites of the arthropods. All procedures must be described and validated. Scientific literature, ideally from peer-reviewed journals, reflecting current scientific knowledge may be used to support the chosen methods. The investigator(s) should use the same validated methods and techniques throughout the trial and be suitably trained to avoid variability and/or bias in assessment and reporting.

Approach to the controlled test:

1. The efficacy of an ectoparasiticide can be determined by comparing the number of ectoparasites on the control animals with the number of ectoparasites on the treated animals after a suitable post-treatment interval.

2. The population of infested animals should be randomly assigned to at least two groups. The method of randomisation and assignment to groups must be described and justified. One group serves as a control group while the other group(s) is treated with the test product. After suitable time interval(s), ectoparasites should be recovered, identified and quantified with an appropriate method.

3. When a controlled clinical trial against temporarily infesting ectoparasite species is to be conducted in pasture animals, the population of animals should be randomly assigned to two groups and placed on similar pastures. Groups of animals should be maintained under such conditions to guarantee comparable parasite exposure and loads but exclude interference between treated animals and controls. Before start of treatment, it must be ensured that the ectoparasite burden is comparable in both control and treatment groups.

4. Abbott's formula should preferably be used to determine efficacy of the product expressed as a relative reduction in parasite counts compared to an untreated control group. The percentage efficacy for each species of ectoparasite is determined by comparing the treated group and control group as follows:

   Efficacy (%) = $100 \times (m_c - m_t) / m_c$

   Where m_c = mean number of ectoparasites in the control group,

   m_t = mean number of ectoparasites in the treated group.

5. Calculation of efficacy should generally be based on arithmetic mean ectoparasite counts irrespective of whether the count data are skewed or not, since efficacy estimates based on geometric means tends to be biased upwards and might potentially mask individual treatment failures. However, efficacy calculation based on geometric mean counts may also be reported. If geometric (i.e. logarithmic) means or other suitably transformed means are used, the transformation must be justified and arithmetic means also presented. Reference should be made to species-specific guidelines where available and more detailed information on acceptable approaches to calculation of efficacy is provided.

6. Results must be statistically analysed and, where possible, confidence limits of the means should be given. The statistical method used must be justified.

7. The difference in counts between treated and untreated animals must be statistically significant at a level of 5% ($p \leq 0.05$).

In general, for most ectoparasites, an overall efficacy of more than 90% is required, but higher thresholds for efficacy may be required depending on the parasite species. For example, efficacy should be at least 95% for *Ctenocephalides canis* and *felis*, approximately 100% for all lice and *Sarcoptes scabiei* and *Psoroptes ovis* infestations.

However, for some ectoparasites lower efficacy thresholds may be permitted, for example, for diptera species (e.g. *Musca* spp. and *Hydrotea* spp.) and larval arthropods, efficacy should be at least 80% and preferably more than 90%. Where indicated and justified, clinical parameters may be used to support efficacy of the product (e.g. *Demodex canis* infestations).

For parasites that only complete part of their life cycle on the animal, treatment should be directed towards elimination of parasitic stages. In the case of the latter, treatment should at least result in resolution of clinical signs or the significant reduction of nuisance. This can be achieved by reducing parasite burdens on the animal to clinically irrelevant levels, by preventing active stages from settling on the host by repelling.

Reference should be made to species-specific guidelines to confirm the efficacy thresholds required for the various ectoparasites and stages associated with the effect being claimed (killing, repellent etc.).

8. Specific requirements

8.1. Products for topical use

Products for topical use include shampoos, aerosols, spot-ons, pour-ons or dust formulations, ear tags, collars, clips, dipping or spray-race formulations, etc.

While the general requirements described above also apply to products for topical use, it is necessary to take into account interactions between treatment and regional climatic, environmental and husbandry conditions as well as animal characteristics during the course of the clinical trial(s). In particular, the applicant should consider the need for additional studies evaluating the effect (if any) of:

a) rainfall (may be mimicked) at various intervals before, during and after treatment,

b) sunshine and hot weather under monitored conditions during and after treatment,

c) dilution (e.g. with dipping),

d) washing or bathing during the treatment period,

e) hair length and thickness of coat,

f) dirtiness of the animal's coat and dirtying of preparations (e.g. of dipping formulations) during the treatment,

g) self-grooming or mutual grooming of treated animals (i.e. unintended removal following application),

h) different body sizes of target animals treated with a standard dose formulation,

i) effects on the quality of fleece or hide and impact on tanning or processing.

The duration of follow-up in the clinical trial(s) should be adequate to monitor for adverse effects of the product. Where secondary pharmacodynamic effects are seen, a study on the dose/effect relationship may be required.

8.2. Insecticide-delivery systems (e.g. collars, ear tags etc.)

If the product is intended to be effective against arthropods with seasonal activity, then the clinical trial(s) must be conducted over the entire season. Evaluation will be based on demonstrating an acceptable level of efficacy against the targeted ectoparasite(s) for the duration to be claimed by comparison with control animals, where relevant. Controls and treated animals should occupy separate lots within the same area throughout the trial. Groups of animals should be maintained under such conditions to guarantee comparable parasite loads but exclude interference between treatments and controls.

8.3. Risk of resistance development

For antiparasitic veterinary medicinal products, information on current prevalence of resistance (if applicable) and on the potential emergence of resistance of clinical relevance for the claimed indication(s) in the target species shall be provided. Where possible, information on the resistance mechanism(s), the molecular genetic basis of resistance, and the rate of transfer of resistance determinants shall be provided in the application dossier for ectoparasiticidal veterinary medicinal products. Measures to limit resistance development shall be proposed.

It may be the case that ectoparasitic resistance varies between geographical locations. When known, the resistance profile of ectoparasites should be described and the location of studies and strains of ectoparasites investigated should take account of resistance profiles to ensure that study findings are representative for the ectoparasites in the EU.

Suspected cases of lack of efficacy observed in the pre-clinical studies or clinical trials should be appropriately discussed.

Further, in order to ensure that studies are appropriately conducted to minimise the risk of resistance development, the bodyweight of animals to be administered the investigational product should be determined as accurately as possible and the dose accurately measured in order to avoid possible under-dosing.

8.4. *Combination veterinary medicinal products*

It is not uncommon for active substances with ectoparasiticidal properties to be combined in a veterinary medicinal product in order to extend the spectrum of activity compared to each individual active substance. However, it is of utmost importance that each active substance to be included in a fixed combination veterinary medicinal product has a documented contribution within the combination. Superfluous administration of a substance in a fixed combination product is considered inappropriate, even if the substance is considered as safe on the basis of target animal tolerance data and when used as indicated. This is of particular importance in terms of ensuring that risks for development of antiparasitic resistance are minimised when more than one active substance is administered in combination. Reference should be made to the CVMP Guideline on pharmaceutical fixed combination products (EMA/CVMP/83804/2005) for more detailed guidance.

In order to ensure appropriate use of fixed combination ectoparasiticidal veterinary medicinal products, the existence and risk of infestation with species of ectoparasites targeted by the active substances included in the combination products should be confirmed, that is, ensure that all active substances are

necessary at the time of administration. Consequently, the SPCs for combination ectoparasiticidal products should be clear that the product should only be used when all active substances are indicated at the same time.

8.5. *Generic/hybrid veterinary medicinal products* – data requirements

Ectoparasiticides can act systemically or locally.

For systemically acting ectoparasiticidal products, it is possible to demonstrate bioequivalence of the candidate and reference products by means of conducting bioavailability studies. For those candidate veterinary medicinal products, bioavailability studies demonstrating bioequivalence with the reference veterinary medicinal product or a justification as to why such studies were not performed (see CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products, EMA/CVMP/016/2000) need to be provided.

For locally acting ectoparasiticidal products, bioavailability studies cannot be used to demonstrate bioequivalence of the candidate and reference products. For those candidate ectoparasiticidal veterinary medicinal products with local activity only and where the same indications compared to the reference product are proposed, the overarching principle is that the candidate product should be therapeutically equivalent to the reference product. To prove therapeutic equivalence and to allow a reduced number of studies and also to avoid unnecessary use of animals in experiments, at least the following data package should be provided:

- The efficacy of the candidate product should be confirmed under laboratory conditions in at least one controlled dose confirmation study for each of the species (stages) of ectoparasites and in each of the proposed target animal species using ectoparasites that are sufficiently representative of the current field situation.
- If only one dose confirmation study is conducted (per species of target ectoparasite and per target animal species), indications cannot be more favourable (for example, longer persistent efficacy claim) than those of the reference product. In case more favourable indications are proposed, adequate pre-clinical and clinical data need to be provided.
- The option to confirm efficacy of a topically applied ectoparasiticide with local activity by using at least one controlled pre-clinical study with the least susceptible ectoparasite species determined *in vitro* can be accepted only if both a validated *in vitro* method exists for the ectoparasite, and a clear correlation between *in vivo* and *in vitro* results is available.
- In general, local tolerance data should be provided according to the requirements of the VICH Guideline on target animal safety for veterinary pharmaceutical products (EMEA/CVMP/VICH/393388/2006).

Efficacy and tolerance studies may not be necessary if the following conditions are fulfilled: the candidate product has the same pharmaceutical form and contains qualitatively and quantitatively the same active substance(s), the excipients of the candidate product are qualitatively and quantitatively the same or very similar compared to the reference product, and the physicochemical properties (e.g. crystalline form, particle size distribution, viscosity, relative density, dissolution profile, release profile) of the candidate product are the same or similar to those of the reference product.

If there is a difference in the qualitative or quantitative composition of the excipients which may affect absorption or the release profile, the rate and extent of distribution and persistence of the active substance, efficacy and tolerance studies may be necessary.

Resistance

For generic veterinary medicinal products containing an ectoparasiticidal substance, information about the level of resistance, as known from bibliographical data, shall be provided; however, generation of new study data is not required.

For hybrid veterinary medicinal products, the risk of development of resistance shall be addressed, if applicable (e.g. for changes in indications or inclusion of new target animal species).

9. General approach to wording of indications in the product information for ectoparasiticidal products

In order to ensure that it is clear to prescribers and users of ectoparasiticidal veterinary medicinal products, precisely which ectoparasite(s) (including development stages) the product has been demonstrated to be efficacious against, a consistent approach to the wording of indications should be utilised in the product information.

It is generally expected that the following information is clearly set out in the indication(s):

- The species of ectoparasite(s) (including development stages, if appropriate) against which an acceptable level of efficacy has been demonstrated in accordance with guideline requirements.
- Information on the time to onset of efficacy e.g. treatment claims supported by demonstrating immediate efficacy (i.e. efficacy against existing infestations).
- Information on the duration of efficacy i.e. claims supported by demonstrating persistent efficacy thereby preventing re-infestation.
- For fixed combination products, to ensure that treated animals harbour, or are at risk from, infestation of mixed ectoparasites necessitating the administration of all active substances included in the fixed combination product, the following wording should be used:

"For <target animal species> with, or at risk from mixed infestations by <ectoparasites targeted by the combination of active substances>. The veterinary medicinal product is only indicated when use against <appropriate arrangement of ectoparasite groups or species> is indicated at the same time."

When the fixed combination product is a combination of an ectoparasiticide with an endoparasiticide, the same requirements to ensuring the need for each of the active substances at the time of administration applies and reference to the wording recommended in the CVMP Guideline on the summary of product characteristics for antiparasitic veterinary medicinal products (EMA/CVMP/EWP/170208/2005) should be made.

For products with a killing or repelling effect, it is considered appropriate that the product information suitably identifies the time point for onset of such an effect (immediate efficacy) following administration of the product as well as the duration of such an effect (persistent efficacy) for which an acceptable level of efficacy against each of the targeted ectoparasites has been demonstrated in accordance with guideline requirements. Imprecise claims such as 'for up to X weeks' should be avoided.

The time-point for the assessment of immediate efficacy after prior infestation with ectoparasites is usually up to 24 or 48 hours post-treatment, depending on the parasite, method of exposure and the effect assessed (acaricidal/insecticidal/repellent). In contrast, the first time-point for assessing efficacy in preventing re-infestation after treatment is usually 7 days but may be longer depending upon the expected duration of persistent efficacy.

The duration of persistent efficacy is defined as the interval between treatment and the last time-point at which efficacy has been appropriately demonstrated.

Information on the time to onset of ectoparasiticidal effect and duration of persistent efficacy is important for various parasites (ticks, fleas, sandflies, mosquitoes etc.) and in particular for parasites which may transmit vector borne pathogens including zoonotic pathogens.

Therefore, the first and last time point of efficacy should both be included in the indications for use as follows:

Prevention of re-infestations with <ectoparasite name, ectoparasite species> through a <type of effect> ***from X days to*** *X weeks after treatment.*

or

Persistent <type of effect> activity ***from X days to*** *X weeks after treatment for <ectoparasite name, ectoparasite species>.*

References

The following legislation and guidelines are relevant to this guideline:

1. Regulation (EU) 2019/6 of the European Parliament and of the Council on veterinary medicinal products repealing Directive 2001/82/EC.
2. Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes.
3. CVMP Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches (EMA/CHMP/CVMP/JEG-3Rs/450091/2012).
4. CVMP Guidelines on specific efficacy requirements for ectoparasiticides in cattle (EMEA/CVMP/625/03).
5. CVMP Guidelines on specific efficacy requirements for ectoparasiticides in sheep (EMA/CVMP/411/01).
6. 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).
7. Questions and answers on the CVMP guideline on the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestations in dogs and cats (EMA/CVMP/EWP/82829/2009).
8. CVMP Guideline on data requirements for veterinary medicinal products intended to reduce the risk of transmission of vector-borne pathogens in dogs and cats (EMA/CVMP/EWP/278031/2015).
9. CVMP Guideline on the summary of product characteristics for antiparasitic veterinary medicinal products (EMA/CVMP/EWP/170208/2005).
10. CVMP Questions and answers on the Guideline on the summary of product characteristics for antiparasitic veterinary medicinal products (EMA/CVMP/EWP/799840/2022).
11. CVMP Reflection paper on resistance in ectoparasites (EMA/CVMP/EWP/310225/2014).
12. CVMP Guideline on statistical principles for clinical trials for veterinary medicinal products (pharmaceuticals) (EMA/CVMP/EWP/81976/2010).
13. CVMP Guideline on pharmaceutical fixed combination products (EMA/CVMP/83804/2005).
14. VICH Topic GL9 – Guideline on Good Clinical Practices (CVMP/VICH/595/98).
15. CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000).
16. Corrigendum to European Commission Notice: Guidance to Applicants – Veterinary Medicinal Products (C/2024/90009).