EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2023
EMA/CVMP/EWP/56030/2023
Committee for Veterinary Medicinal Products (CVMP)

Concept paper on the revision of the guideline for the demonstration of efficacy of ectoparasiticides

Agreed by the CVMP's Efficacy Working Party (EWP-V)	June 2023
Adopted by the Committee for Veterinary Medicinal Products (CVMP) for release for consultation	13 July 2023
Start of public consultation	21 July 2023
End of consultation (deadline for comments)	31 October 2023

The proposed guideline will replace the current "Guideline for the 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

Keywords	***Ectoparasites, veterinary medicinal products, ectoparasiticides, efficacy***

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1. Introduction

The current guideline for veterinary medicinal products for the demonstration of efficacy of ectoparasiticides (7AE17a) was adopted in September 1994. The objective of this guideline is currently stated as *"to provide specific guidance in respect of the documentation of the efficacy of ectoparasiticides. It should be read in conjunction with Directive 81/852/EEC as amended, and the note for guidance on Good Clinical Practice for the conduct of clinical trials on veterinary medicinal products in the European Union".*

The current guidance document addresses the general data requirements to support the efficacy of ectoparasiticidal veterinary medicinal products and sets overall efficacy thresholds and the method used to calculate efficacy.

The current guidance outlines the general requirements in terms of the type(s) of (pre-)clinical studies to be submitted in support of efficacy and gives special recommendations for products used topically and for prolonged delivery systems such as collars.

There are also currently three species-specific guidelines that set out data requirements to demonstrate efficacy of ectoparasiticides in cattle, sheep, dogs and cats, namely,

- Guidelines on specific efficacy requirements for ectoparasiticides in cattle (EMEA/CVMP/625/03-Rev.1)
- Guidelines on specific efficacy requirements for ectoparasiticides in sheep (EMA/CVMP/411/01-Rev.1)
- 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.4).

2. Problem statement

Given that scientific knowledge has developed since the current guideline for veterinary medicinal products on the demonstration of efficacy of ectoparasiticides (7AE17a) was adopted in September 1994 and also given the changes in regulatory requirements and the experiences gained in assessment of data submitted for the purpose of demonstrating efficacy of ectoparasiticidal products, it is considered appropriate that the current guideline is updated. In particular, the guidance document should be updated to use more up-to-date terminology, for example, by replacing reference to terminology such as 'control' of infestations, or 'dose titration'.

In addition, it is considered appropriate that the guidance is updated to include reference to current legislation, relevant guidelines and the 3Rs principles (Replacement, Reduction and Refinement) when designing/conducting efficacy studies. Specifically, the guidance document also requires updating to ensure consistency with the definitions provided in Regulation (EU) 2019/6 and the content of Annex II to Regulation (EU) 2019/6.

Considering the need to reduce the risk of development of antiparasitic resistance, it is considered appropriate that the guidance is updated to take into consideration factors that may affect risk for resistance development and to provide recommendations for minimising such risks when designing and conducting pre-clinical efficacy studies and clinical trials.

Approaches to calculate and assess efficacy (use of arithmetic mean, geometric mean or other suitable measure of central tendency and selection of appropriate efficacy thresholds) should preferably be clarified so that a consistent approach to the presentation and subsequent assessment of efficacy data is ensured.

Also, guidance relevant to demonstrate efficacy of combination ectoparasiticidal products should be included.

It is recommended that the revised guideline will also provide as far as is possible, recommendations on adopting a consistent approach to the wording of indications for comparable products in order to facilitate user understanding of the efficacy that has been demonstrated for the concerned products and their correct use. In addition, the revised guideline should provide recommendations 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.

As there are a number of species-specific CVMP guidelines already available that set out detailed efficacy requirements for cattle, sheep, dogs and cats, it is considered appropriate that the current guideline for veterinary medicinal products for the demonstration of efficacy of ectoparasiticides should be kept at a general level to be read in conjunction with species-specific guidelines which provide more detailed guidance and information. However, it is proposed that the title of the guideline will be updated to a more appropriate title, such as 'Guideline for the evaluation of efficacy of ectoparasiticides - general requirements'.

It would also be beneficial to clarify the approach in case of generic/hybrid antiparasitic veterinary medicinal products for which bioavailability studies cannot be used to demonstrate bioequivalence.

3. Discussion (on the problem statement)

As the current guideline for veterinary medicinal products for the demonstration of efficacy of ectoparasiticides (7AE17a) was adopted two decades ago (September 1994), it is considered appropriate that the guideline is updated to reflect current scientific knowledge and regulatory practices. The experiences gained in the submission and assessment of data for ectoparasiticidal veterinary medicinal products should be taken into account when updating the guideline.

The thresholds for efficacy cited in the guideline are not fully consistent with those mentioned in some of the species-specific CVMP guidelines and should therefore be harmonised and updated accordingly.

Reference is made to outdated legislation (Directive 81/852/EEC) and use is made of terminology that is no longer consistent with the definitions and terminology used in Regulation (EU) 2019/6 or its Annex II. For example, reference is made to the 'control of infestations' whereas more suitable terminology consistent with current assessment practices and approved indications should be used. Consequently, the guideline requires updating to refer to and be consistent with current legislation, regulatory requirements, definitions and terminology.

Cross-references to other applicable technical and scientific guidelines will be made.

Given the intention to take into account the 3Rs principles in the EU as detailed in Directive 2010/63/EU and as stated in the EMA position on the application of the 3Rs in the regulatory testing of human and veterinary medicinal products, it is considered appropriate that the guideline is updated to include reference to those principles when considering the design and conduct of studies to be submitted in support of the evaluation of efficacy of ectoparasiticidal veterinary medicinal products.

In accordance with Article 4(19) of Regulation (EU) 2019/6, the risk relating to the development of resistance is part of the evaluation of the 'benefit-risk balance' of a product, which will be reflected in the product information. Therefore, the product information should include provisions regarding the use of antiparasitic veterinary medicinal products in order to limit the risk of development of resistance. Furthermore, section II.4A2 of Annex II to Regulation (EU) 2019/6 indicates that information on current resistance (if applicable) and on the potential emergence of resistance of clinical

relevance for the claimed indication in the target animal species shall be provided as part of an application for a marketing authorisation for an antiparasitic veterinary medicinal product. Consequently, it is considered appropriate that the guideline should include general guidance on factors that may affect risk for resistance development and provide recommendations on how to take account of those factors to minimise risk of resistance development when designing and conducting pre-clinical efficacy studies and clinical trials.

The current guideline indicates that efficacy may be calculated using the arithmetic mean, the geometric mean or other suitably transformed mean (providing such transformation is suitably justified), whereas species-specific guidelines are more prescriptive on this aspect with some prescribing that efficacy should be determined based on arithmetic means. To ensure a consistent approach to the evaluation of efficacy of ectoparasiticidal veterinary medicinal products, it is considered appropriate that the guideline is updated to ensure consistency with species-specific CVMP guidelines and accepted regulatory approaches to demonstrating efficacy.

Given the interest in developing combination veterinary medicinal products that include ectoparasiticidal active substances, it is recommended that the guideline is updated to provide guidance on the general approach to evaluating efficacy of such ectoparasiticidal products and in particular, on the necessity to ensure that the intended use of such products avoids superfluous administration of active substances and thereby minimises unnecessary exposure to active substances that may, as a consequence, contribute to the development of antiparasitic resistance.

In light of the experience gained since the publication of the current guideline, it is evident that indications for comparable products may sometimes differ substantially (unnecessarily). It is recommended that the revised guideline will consider as far as is possible, recommendations on adopting a consistent approach to the wording of indications in order to ensure consistency between product information and to facilitate user understanding of the efficacy that has been demonstrated for the concerned products. That is, where possible, a consistent approach to the wording of indications should be recommended. As part of this consideration, it is proposed that general guidance on the approach to evaluating the onset of efficacy and the duration of efficacy for the prevention of re-infestations should be provided where appropriate in order to make it clear to the prescriber/user as to the expected efficacy of the product.

In the case of generic/hybrid antiparasitic veterinary medicinal products for which bioavailability studies cannot be used to demonstrate bioequivalence, it is proposed that the guideline provides clarification on the number and type of studies required to demonstrate efficacy of the product.

4. Recommendation

The CVMP recommends the revision of the existing guideline for the demonstration of efficacy of ectoparasiticides (7AE17a) in order to provide clearer guidance and to align the guideline with current scientific and regulatory requirements, as outlined above.

5. Proposed timetable

21 July 2023	Concept paper released for consultation
31 October 2023	Deadline for comments from interested parties
Q2 2024	Expected date for adoption of the draft revised guideline by CVMP for release for consultation
Q4 2024	Expected end of consultation on the draft revised guideline
Q2 2025	Expected date for adoption by CVMP and publication of the revised guideline

6. Resource requirements for preparation

Revision of the guideline will involve two EWP-V rapporteurs and three co-rapporteurs.

Preparation of the draft revised guideline will require discussion at two EWP-V plenary meetings. Drafting group meetings (virtual) will be organised, as needed.

7. Impact assessment (anticipated)

The revision of the guideline is expected to improve the guidance for applicants as well as for regulatory authorities. It is not intended to increase the requirements for marketing authorisation applications for veterinary medicinal products.

8. Interested parties

- Veterinary pharmaceutical industry and regulatory consultants;
- EU regulatory authorities involved in the assessment of marketing authorisation applications for veterinary medicinal products;
- Veterinary organisations and professional bodies;
- Scientific veterinary associations.

9. References to literature, guidelines, etc.

Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC

Guideline for the Demonstration of efficacy of ectoparasiticides (7AE17a)

Guidelines on specific efficacy requirements for ectoparasiticides in cattle (EMEA/CVMP/625/03-Rev.1)

Guidelines on specific efficacy requirements for ectoparasiticides in sheep (EMA/CVMP/411/01-Rev.1)

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.4)

Guideline on the summary of product characteristics for antiparasitic veterinary medicinal products (EMA/CVMP/EWP/170208/2005-Rev.1)

Questions and answers on the 'Guideline on the summary of product characteristics for antiparasitic veterinary medicinal products' - EMA/CVMP/EWP/170208/2005-Rev.1 (EMA/CVMP/EWP/799840/2022)

Guideline on statistical principles for clinical trials for veterinary medicinal products (pharmaceuticals) (EMA/CVMP/EWP/81976/2010-Rev.1)

Good Laboratory Practice (GLP) (see Directive 2004/9/EC and Directive 2004/10/EC)

VICH Topic GL9 (GCP): Guideline on Good Clinical Practices (CVMP/VICH/595/1998)

Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches (EMA/CHMP/CVMP/JEG-3Rs/450091/2012)

Q&A document on requirements for pre-clinical studies submitted in support of a marketing authorisation application for a veterinary medicinal product (EMA/CVMP/565615/2021-Rev.1)