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Committee for Veterinary Medicinal Products (CVMP)

Concept paper on the revision of the guideline on veterinary medicinal products controlling *Varroa destructor* parasitosis in bees

Agreed by Efficacy Working Party (EWP-V)	June 2024
Adopted by CVMP for release for consultation	18 July 2024
Start of public consultation	26 July 2024
End of consultation (deadline for comments)	31 October 2024

The proposed guideline will replace the current "Guideline on veterinary medicinal products controlling *Varroa destructor* parasitosis in bees" (EMA/CVMP/EWP/459883/2008-Rev.1).

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

Keywords	*Varroosis, honeybees, efficacy, veterinary medicinal products, capped brood.*

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1. Introduction

The CVMP guideline on veterinary medicinal products controlling *Varroa destructor* parasitosis in bees (EMA/CVMP/EWP/459883/2008) was initially adopted in July 2008, with the last revision (Rev.1) carried out in July 2021 to implement administrative changes in order to align the guideline to Regulation (EU) 2019/6.

This concept paper addresses the need for a comprehensive revision of the guideline. The revision will be based on points for improvement raised by a stakeholder contemplating the development of new veterinary medicinal products (VMPs) for the treatment of varroosis, but also more generally, on other points reviewed in the light of current scientific knowledge in the field and on regulatory experience.

In general, due to the efficacy of new active substances or VMPs with different mechanisms of action and/or physico-chemical properties, it is necessary to address methods and special considerations when designing study protocols that are better suited to the modes of action of these substances or VMPs. In addition, owing to the risk of emergence of resistance to existing substances, it is considered appropriate to support potential new substances or products to obtain a marketing authorisation.

2. Problem statement

This guideline aims to provide general guidance on aspects that should be considered or addressed when designing and conducting studies aimed at demonstrating efficacy and target animal safety for VMPs intended for varroosis control in honey bees.

The assessment of the efficacy in the current guideline is mainly focused on products targeting dispersal-phase mites and on the mortality of *Varroa* based on the count of mite fall as part of a critical test. Thus, the efficacy and safety of VMPs with particular physical properties, such as vaporous acaricides that may penetrate below brood cappings, or products which have a longer-term impact on the dynamics of mite populations (e.g. products interfering with reproduction) may not be adequately addressed. Therefore, the revision of the guideline in order to include additional methods taking into account these properties to assess the efficacy should be considered.

In addition, some sections of the guideline should be updated in order to incorporate the information included in the Q&A document (EMA/CVMP/EWP/77872/2018) on the follow-up treatment and the evaluation of safety in queens. Moreover, certain other sections of the guideline could be revised, e.g. to better explain the function of negative control colonies in the evaluation of the efficacy.

Finally, as several other related guidelines have been recently developed, e.g. Guideline on efficacy and target animal safety data requirements for applications for non-immunological veterinary medicinal products intended for limited markets submitted under Article 23 of the Regulation (EU) 2019/6 (EMA/CVMP/52665/2020) or Guideline on efficacy and target animal safety data requirements for applications for non-immunological veterinary medicinal products intended for limited markets but not eligible for authorisation under Article 23 of Regulation (EU) 2019/6 (EMA/CVMP/EWP/231668/2022), it should be ensured that the guideline on VMPs controlling *Varroa destructor* parasitosis in bees is in line with those other linked guidance documents.

3. Discussion (on the problem statement)

The lack of different and more flexible approaches in certain sections of the current guideline may lead to challenges in inadequate assessment of target animal safety and efficacy for some VMPs. For example, historically, varroacides have been products targeting dispersal-phase mites. Vaporous acaricides, such as

formic acid and thymol, have physical properties distinct from contact chemicals, and these may require special consideration when designing study protocols.

In particular, the following points should be noted:

- Vaporous acaricides depend on the maintenance of a minimum dose of active substance inside the hive to be effective. However, unlike for contact chemicals, airflow through the hive can alter the dose of vaporous acaricides. Thus, airflow through hive during efficacy testing should be in accordance with the intended instructions for use.
- The current guideline includes only one means of determining product efficacy: mortality of *Varroa* based on mite fall on bottom boards. It may be useful to also include supplementary methods, such as those based on estimating infestation rates in adult bees before and after treatment (e.g. ethanol washes or powdered sugar shakes) to support product authorisation.
- Moreover, some active substances like vaporous acaricides may be effective in capped brood, killing reproductive-phase as well as dispersal-phase *Varroa* [1]. The guideline currently does not contain a recognised method for assessing efficacy of varroacides causing mortality within capped brood cells. This could be important as, according to some references, a significant percentage of the *Varroa* population within a colony may be located within capped brood cells [2].
- Additionally, in certain cases it could be useful to understand longer-term impact of acaricides in honeybee colonies, e.g. those interfering with the reproductive capacity of the mites. Although the guideline includes guidance on conducting long-term monitoring of colony strength parameters, it does not currently include methods of assessing long-term effects of treatments on *Varroa* population dynamics.
- In the current guideline, it is not clearly explained how the control colonies should be used in the efficacy assessment at the different stages of clinical product development, taking into account that, basically, the efficacy percent is calculated only for the treated colonies using the follow-up treatment.
- The guideline should also be in alignment with current recommendation for 3Rs principles and animal welfare testing approaches.

Consequently, the following items should be considered in the current revision of the guideline:

- Consider the need to highlight the importance of tightly-fitting equipment when conducting efficacy testing on vaporous acaricides and airflow through the hive as it can alter the dose of these products.
- Consider the need to include in the current guideline supplementary methods to evaluate the efficacy, such as methods based on estimating infestation rates in adult bees [3] before and after treatment, methods to assess the efficacy in capped brood, or methods to evaluate the long-term effects [4] of acaricides on *Varroa* population dynamics.
- Consider the role of the control colonies at different stages of clinical product development and the efficacy calculates.
- Reconsider the current recommendations regarding efficacy thresholds (minimum percentages of mite count reduction), which might not be adapted anymore to the range of new substances, products or indications that are or will be developed.
- Align the guideline with current scientific and regulatory requirements, including 3Rs principles and animal welfare.

Furthermore, considering the current scientific knowledge, other sections of the current guideline could be open to revision, if appropriate.

4. Recommendation

The CVMP recommends the revision of the existing guideline on veterinary medicinal products controlling *Varroa destructor* parasitosis in bees in order to provide clearer guidance and to align the guideline with current scientific and regulatory requirements, taking into account the issues identified above.

5. Proposed timetable

July 2024	Concept paper released for public consultation
31 October 2024	Deadline for comments from interested parties
Q2 2025	Expected date for adoption of the draft revised guideline by CVMP for release for consultation
Q4 2025	Expected end of consultation on the draft revised guideline
Q2 2026	Expected date for adoption by CVMP and publication of the revised guideline

6. Resource requirements for preparation

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

The preparation of the draft revised guideline will require discussion at several 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 such veterinary medicinal products.

8. Interested parties

- Veterinary pharmaceutical industry and 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.

[1] Fries, I. (1991). Treatment of sealed honey bee brood with formic acid for control of *Varroa jacobsoni*. American Bee Journal, 131(5), 313-314.

[2] Wilde, J., Fuchs, S., Bratkowski, J., & Siuda, M. (2005). Distribution of *Varroa destructor* between swarms and colonies. Journal of Apicultural Research, 44(4), 190-194.

[3] Dietemann, V., Nazzi, F., Martin, S. J., Anderson, D. L., Locke, B., Delaplane, K. S., ... & Ellis, J. D. (2013). Standard methods for varroa research. Journal of Apicultural Research, 52(1), 1-54.

[4] Faber, N. R., Meiborg, A. B., Mcfarlane, G. R., Gorjanc, G., & Harpur, B. A. (2021). A gene drive does not spread easily in populations of the honey bee parasite *Varroa destructor*. Apidologie, 52(6), 1112-1127.