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Concept paper on a Guideline on data requirements for post-authorisation studies for antimicrobial veterinary medicinal products under Article 36(2) of Regulation (EU) 2019/6

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

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Concept paper on a Guideline on data requirements for post-authorisation studies for antimicrobial veterinary medicinal products under Article 36(2) of Regulation (EU) 2019/6

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1. Introduction

The CVMP's work plan for 2022 [1] includes several activities intended to implement the measures introduced in Regulation (EU) 2019/6 [2] directed at the problem of antimicrobial resistance (AMR). Amongst these activities there is a proposal to develop a concept paper on requirements for post-authorisation studies (PAS) for antimicrobial veterinary medicinal products (VMPs) in order to ensure the benefit-risk balance remains positive in case of development of antimicrobial resistance, as laid out in Article 36(2) of the Regulation. This action is likewise included in the CVMP's Strategy on Antimicrobials 2021–2025 [3] under Aim 3, relating to measures to ensure the on-going availability and effectiveness of authorised veterinary antimicrobials.

2. Problem statement (motivation to develop the concept paper)

In relation to decisions granting marketing authorisations, Regulation (EU) 2019/6 of the European Parliament and of the Council lays down in Article 36(2) [2]: *"Where the application concerns an antimicrobial veterinary medicinal product, the competent authority or the Commission, as applicable, may require the marketing authorisation holder to conduct post-authorisation studies in order to ensure that the benefit-risk balance remains positive given the potential development of antimicrobial resistance."*

Annex II of Regulation (EU) 2019/6 does not provide guidance on the specific circumstances when post-authorisation studies are required or on the type of data to be submitted to fulfil the obligation in Article 36(2). Thus, a scientific guideline should be developed to provide an EU harmonised approach to this regulatory provision.

A CVMP reflection paper on antimicrobial resistance surveillance as post-marketing authorisation commitment was published by EMA in 2008 [4]. This document considered the circumstances when such data should be requested as well as the methodologies and data sources that could be used and will be useful background for the elaboration of new guidance.

As some time has elapsed since development of the reflection paper, and there is now a legal basis for the competent authority or the Commission to require PAS studies on AMR, it is proposed that a new guideline should be provided. In the guideline, all types of antimicrobials (i.e. antibiotics, antifungals, antivirals and antiprotozoals) should be considered.

3. Discussion (on the problem statement)

Article 36(2) states that, when the application concerns an antimicrobial VMP, the marketing authorisation holder may be required to conduct PAS in order to ensure that the benefit-risk balance remains positive. By taking into account that AMR development is a dynamic process, it should be outlined in the objectives of the guideline under which circumstances these additional data might be required (at the time of authorisation) and what kind of data need to be collected (post-authorisation). The guideline should take also into account the new definitions and provisions of Regulation (EU) 2019/6, such as the definition of antimicrobial (includes antibiotics, antifungals, antivirals and antiprotozoals Article 4(11)), and of benefit-risk balance Article 4(19). The benefit-risk balance concept has been revised and includes that an evaluation of the positive effects of a VMP should be considered in relation to the risk of development of resistance in addition to other risks relating to the use of the product.

Since the requirement for post-authorisation studies under Article 36(2) is at the discretion of the national competent authority or the Commission, specific guidance should be provided on the circumstances for this requirement, e.g. for:

- new classes of drugs or existing classes of antimicrobials with extended or altered spectrum of activity where the documentation provided prior to marketing authorisation could not cover all aspects of importance when assessing the risk for development of resistance;
- new molecules within an existing class where the mode of action and spectrum of activity are similar to existing molecules;
- existing molecules where there is a new target pathogen/indication;
- considerations relevant to specific legal types of applications e.g. generics, hybrids, combinations, informed consent, etc;

The CVMP has published specific guidance for antimicrobials, which might need to be taken into consideration for the establishment of the guideline [4-10].

The methodologies (e.g. monitoring/surveillance MIC studies) and data sources (sponsored/public activities) outlined in the CVMP reflection paper [4] should be reviewed to determine if they are still up to date and are sufficiently addressing the provisions of Article 36(2) in order to implement them into the guideline. Therefore, it has to be considered which specific studies would be relevant for determining the impact of AMR on the benefit-risk balance e.g. passive monitoring, pro-active surveillance, epidemiologic surveys (e.g. outbreak reports such as from EpiPulse). Potential sources of information should consider, but are not limited to, surveillance data with standardised investigation strategies and comparable interpretation criteria (EUCAST/VetCAST, CLSI). Outbreak and early warning reports from both human, animal, zoonotic and environmental sources, could be referred to wherever possible, also outside Europe.

AMR risks may relate to animal health and/or public health and/or to the environment as outlaid in Article 8(2). Thus, the guideline should provide clarification on which organisms should be covered by PAS e.g. target animal pathogens, food borne pathogens and/or indicator commensal organisms, pathogens relevant for the environment, according to the hazards identified for the concerned antimicrobial VMP. Accordingly, different studies could be meaningful, such as genetic data on resistance mechanism(s), findings on new resistance genes/mechanisms, information on transferability of resistance genes, cross/co-resistance, effects on the microbiota, sudden changes or trends of change in antimicrobial sales/use data. Also new methodologies should be taken into account e.g. Whole Genome/Next Generation Sequencing WGS/NGS data, collection of Real World Data (RWD), Real World Evidence (RWE) [11].

When considering the data requirements, potential sources (e.g. bibliographic/proprietary/sponsored data) and the quality of data (coverage, accuracy of reporting, peer reviewed, expert reports etc.) should also be taken into account.

Further clarification should be provided as regards the appropriate and achievable timeline(s) for the submission of PAS in order to monitor for potential changes in the risk due to development of AMR.

4. Recommendation

The CVMP recommends to develop a "Guideline on data requirements for post-authorisation studies for antimicrobial veterinary medicinal products under Article 36(2) of Regulation (EU) 2019/6", taking into account the issues identified above.

As the guideline should consider possible requirements for antibiotics, antifungal, antiviral and antiprotozoal products, the CVMP's AWP, EWP-V and if necessary, ERAWP should collaborate.

The guideline should contain information on:

- Objectives, scope, legal basis, definitions (Article 4)
- Circumstances when PAS are required
- Studies relevant to determining impact of AMR on the benefit-risk balance and their data requirements
- Data sources and quality
- Timelines for conducting and reporting the studies

5. Proposed timetable

16 September 2022	Concept paper released for consultation
31 January 2023	Deadline for comments from interested parties
Q2 2024	Guideline released for consultation

6. Resource requirements for preparation

The development of the guideline will involve AWP and EWP-V rapporteurs and ERAWP, as needed.

Drafting group (physical and virtual) meetings will be organised.

7. Impact assessment (anticipated)

The guideline will provide information on the specific circumstances when post-authorisation studies are required and up-to-date guidance on the type of data to be submitted to fulfil the obligation in Article 36(2). This will contribute to the effective application of Article 36(2), taking into account the aims of the Regulation in respect of mitigation of the risks of AMR development. It will facilitate the practical and harmonised application of Article 36(2) by regulatory authorities and industry.

8. Interested parties

Veterinary pharmaceutical industry, consultants, EU national competent authorities, veterinarians, antimicrobial users.

9. References to literature, guidelines, etc.

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