21 February 2025
EMA/CVMP/EWP/377613/2024
Committee for Veterinary Medicinal Products (CVMP)

Overview of comments received on 'Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances' (EMA/CVMP/627/2001-Rev.2)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	PETA Science Consortium International e.V.
2	Federation of Veterinarians of Europe (FVE)
3	FAIRR Initiative
4	Access VetMed

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1. General comments – overview

Stakeholder no.	General comment	Outcome (if applicable)
1	PETA Science Consortium International e.V. (the Science Consortium) welcomes the opportunity to comment on this draft guideline. The Science Consortium advances robust non-animal testing methods that protect human health and the environment. We are a member of the International Council on Animal Protection in Pharmaceutical Programs (ICAPPP), an organisation founded in 2005 to promote the use of non-animal approaches in pharmaceutical testing guidelines worldwide.	Thank you for your comments.
2	FVE supports the draft guideline which aligns the text with the new definitions and terminology of Regulation 2019/6.	Thank you for your comments.
3	**1. Antimicrobial Resistance (AMR) Considerations** **Section 6.1.5 (Antimicrobial Resistance)** (p. 7): • This section rightly addresses AMR, which is a key concern in livestock production. We encourage the EMA to consider including more explicit requirements for ongoing post-market AMR surveillance. It has been estimated that **73% of antibiotics sold globally are used in food-producing animals**, raising concerns of significant contribution of this sector to the development of AMR. Ongoing data collection on the development of resistance would enhance understanding and mitigation of AMR risks over time. **2. Prophylactic Use of Antimicrobials**	Thank you for your comments. Responses to individual questions have been provided below. However, please note that the scope of the current revision was to align the guideline to Regulation (EU) 2019/6 and especially Article 4. While the comment is appreciated, any further in-depth amendments, especially pertaining to new requirements, are not foreseen within this revision. However, the comment will be considered in the context of the next revision of the guideline.

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	Section 7.9 (Special considerations for prophylaxis claims) (p. 17): • FAIRR welcomes the guidance provided regarding prophylaxis under **Article 107(3) of Regulation (EU) 2019/6** where prophylaxis can only be administered to food-producing animals in specific conditions where the risk of infection is significant and justifiable and based on a veterinary prescription after thorough assessment of the situation. This is positively viewed by FAIRR as the regulation's alignment goes towards supporting the WHO guidelines Recommendation 3, which "recommends complete restriction of use of all classes of medically important antimicrobials in food-producing animals for prevention of infectious diseases that have not yet been clinically diagnosed". However, EMA may consider clearer guidance for applicants on what constitutes 'significant risk' in prophylaxis scenarios. • As the revised EU Regulation (EU) 2019/6 guidance already states that prophylactic use is restricted to cases where no alternatives are available, it implies that antibiotic alternatives should have been assessed beforehand. The EMA could further strengthen this area, by requiring applicants to provide explicit evidence or documentation showing that non-antibiotic alternatives were thoroughly assessed and found insufficient before prophylactic use is considered. **3. Metaphylaxis Use**	

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	Section 7.8 (Special considerations for metaphylaxis claims) (p. 16): • Metaphylaxis is an important tool in managing disease outbreaks but can also drive excessive antimicrobial use. The new regulations under **Article 107(4) of Regulation (EU) 2019/6** already impose stricter controls on metaphylaxis use, which is that it is only allowed when an infection is already present in part of the group, with a high risk of spread, and only under veterinary prescription. The EMA may consider clearer guidance for applicants on what constitutes 'high risk' in metaphylaxis scenarios, rather than generalised risks assessments or suggestive language. Defining criteria such as the size of the group at risk, environmental factors, or the failure of other control measures could ensure metaphylaxis is only used when absolutely necessary. This could also prevent extensive exceptions for metaphylactic use which are sometimes exploited to justify prophylactic-like practices. AMR poses a significant global threat, with studies suggesting it could lead to a 3.8% decline in global GDP and 8.2 million associated deaths annually by 2050. Limiting metaphylactic use only to situations with strong evidence of imminent disease spread could mitigate these risks. **4. Dose Determination Studies** **Section 6.2.2 (Dose determination studies)** (p. 9): • The current guidance on dose determination is robust, though the EMA may want to consider encouraging	

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	companies to demonstrate how their proposed dosages minimize the risk of AMR development. Research emphasises the importance of using the lowest effective dose to limit resistance and improve health outcomes, and studies show that incorporating pharmacokinetic/pharmacodynamic (PK/PD) modelling - which describe how drug concentrations change over time and how that affects pathogen growth - prove valuable when optimizing dosage for drug treatment of bacterial infections, and thus better avoidance of resistance. **5. Transparency in Summary of Product Characteristics (SPC)** **Section 8 (Summary of Product Characteristics (SPC)** (p. 17): • We welcome the existing SPC guidance and suggest that it could be beneficial to include information on AMR risk, including any resistance patterns observed in clinical trials. FAIRR's engagement with companies has shown that transparency on antimicrobial use is critical for investors. Including this data in the SPC could help stakeholders better assess the sustainability of the product and its long-term risk profile. Sections such as **6.1.5 (Antimicrobial resistance)** and **7.9 (Special considerations for prophylaxis claims)** outline areas that would alleviate concerns of the development and spread of AMR, which is a financially material risk to the global investor community. The document's emphasis on responsible antimicrobial use, efficacy monitoring, and transparency aligns with investor concerns around regulatory compliance, long-term sustainability in food production, and reducing financial risks from AMR-related	

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	disruptions in the supply chain. For example, the World Bank estimates that economic losses to agriculture and trade as a result of AMR could result in a 7.5% decrease in the value of global livestock production from current levels. In this context, the EMA's guidelines play an important role in supporting investors' efforts to mitigate the financial risks posed by AMR, ensuring both regulatory compliance and the long-term resilience of the global food and agricultural sectors.	
4	Thank you for the opportunity to provide comments to this revised guideline. In comparison with the previous version, we do not have comments to make on the changes but one main issue remains regarding its scope. It would be of great advantage for all (applicants and competent authorities) if the guideline could determine whether it (as a whole or in parts) is considered applicable to generic applications. The justification for asking generic applications to provide some of the information detailed in this guideline, such as reviewing any currently available data on resistance prevalence of the target organisms for example, can be supported. But as it was stated in the "Draft guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances - Revision 1 (first version)" (EMA/CVMP/261180/2012), the guideline should not be not meant to address applications for generic products when according to current legislation efficacy studies for those applications are not required. Without a clear statement on the scope of the guideline concerning applicability to generic products it will be left to individual member states CAs to decide how and which parts they apply to generic	Thank you for your comments. We agree that the scope of the guideline should be clear about the type of applications it is applicable to. Under 'scope' it is stated that "*This guideline applies to **all** veterinary medicinal products containing antimicrobial substances…*", which indicates that the guideline is also applicable to generic product applications. Moreover, it is clarified in the scope that the guideline '*applies to all applications where, according to Regulation (EU) 2019/6, new data has to be generated to support clinical efficacy*'. This should be clear enough to applicants and other stakeholders and it is not considered useful to single out certain application types in the general scope. Nonetheless, where Regulation (EU) 2019/6 indicates specific requirements for certain application types, this has been reflected as best as possible in the respective sections of the guideline, e.g. 6.1.5. Antimicrobial resistance: "*…For applications for **generic** veterinary medicinal products containing antimicrobial substances, information about the*

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	applications – which it is anticipated is going to lead to divergence between states in interpretation and application. Without specific guidance on which recommendations are applicable for generic applications there is the potential for NCAs to start asking for increasing amounts of efficacy data, despite this not being required for generics by Regulation 2019/6 on veterinary medicines. This could make approval of generic applications very difficult, expensive or even impossible (particularly with reference products with wide ranging uses not identifying specific pathogens).	*level of resistance, as known from bibliographic data, shall be provided.*" Although the CVMP is not in the position to comment on the approach potentially taken by NCAs towards generic applications, it is generally understood that NCAs will refer to CVMP guidelines. As mentioned above, the guideline applies to applications where, according to Regulation (EU) 2019/6, new data has to be generated to support clinical efficacy.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
92-93 240	4	**Comment**: Please refer to general comment and request for clarification of scope and conditions for generic registrations. This is particularly challenging when the reference product still has general claims, without defined target pathogen specie(s) or indications (i.e. 'treatment of respiratory tract', 'gastrointestinal and urogenital infections', 'infections secondary to viral diseases and septicaemia', 'antibiotic with an activity on a broad spectrum of bacteria', etc..). Experience with such cases during decentralised procedures is complex, since several NCAs request for a list of target pathogens in the SPC, which are not always available for the reference product, this leading to substantial disharmonisation of requirements and criterial from the various NCAs, with significant impact on the applicant and on the procedure with respect to the content of the indications. **Proposed change**: Access VetMed understand some of these issues are of regulatory nature and may not fall under CVMP remittance; still, these are very important aspects and scope clarification in the revised guideline would be very welcome.	Not accepted. Please refer to the response provided under the general comments section above. No changes to the guideline text are considered necessary. General considerations for the preparation of the SPC for antimicrobial products are available in the 'Guideline on the summary of product characteristics (SPC) for veterinary medicinal products containing antimicrobial substances' (EMA/CVMP/383441/2005) (link).
141	1	**Comment:** We suggest strengthening the language regarding the legal requirement to abide by the 3Rs principle set out in Directive 2010/63/EU. Therefore, we suggest prioritising methods that	Not accepted. The current wording is aligned with Regulation (EU) 2019/6 and is therefore considered appropriate and

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		do not use animals and conducting these according to specific practical guidelines. **Proposed change:** Methods that do not use live animals must be prioritised. Where appropriate, these methods should be conducted following Good In Vitro Method Practices (GIVIMP; see OECD Guidance No. 286).	sufficient. No changes to the guideline text are considered necessary.
226 **Section: 6.1.5 (Antimicrobial resistance)** (p. 7)	3	**Current Text:** "The responsible use of antimicrobials should be promoted to prevent the development of antimicrobial resistance." **Proposed change**: Suggest changing "should be promoted" to "**must** OR **is expected to be demonstrated by applicants** through specific strategies aimed at minimizing antimicrobial resistance, including the use of post-market surveillance and ongoing monitoring." This change enhances accountability by requiring applicants to show active efforts in responsible antimicrobial use, rather than simply promoting it.	Not accepted. The current wording is aligned with Regulation (EU) 2019/6 and is therefore considered appropriate and sufficient. Please note that section 6.1.5 'Antimicrobial resistance' does not make specific reference to promoting the responsible use of antimicrobials. No changes to the guideline text are considered necessary.
325 **Section: 6.2.2 (Dose determination**	3	**Current Text**: "The applicant should provide studies to determine the appropriate dosage." **Proposed change:** Strengthen this to: "The applicant **must** OR **is expected** provide studies to determine the minimum effective dosage necessary to achieve efficacy while minimizing the risk of	Not accepted. The current text included in section 6.2.1 'General principles' ('*Appropriate data shall be provided to justify the proposed dose, dosing interval, and duration of treatment'*) is considered appropriate. No changes to the guideline text are considered necessary.

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studies) (p. 9)		antimicrobial resistance, supported by pharmacokinetic/pharmacodynamic (PK/PD) modelling." This language reinforces the need to avoid overuse by focusing on the minimum effective dose and incorporating resistance mitigation strategies into dose determinations.	
346	1	**Comment:** To abide by the 3Rs principle set out in Directive 2010/63/EU, we suggest changing the order of priority of animals used in dose determination studies. Specifically, we suggest prioritising naturally infected animals, if available, that might potentially benefit from the study instead of experimentally inducing infections in additional animals, thereby reducing the total number of animals used. **Proposed change:** Where possible, naturally infected animals potentially benefitting from the studies, ~~experimentally induced infections~~ should be used in the dose determination studies under well controlled study conditions. Experimentally infected animals should only be used as a last resort if those infected naturally are unavailable.	Not accepted. The scope of the current revision was to align the guideline to Regulation (EU) 2019/6 and especially Article 4. While the comment is appreciated, any further in-depth amendments, especially pertaining to new requirements, are not foreseen within this revision. However, the comment will be considered in the context of the next revision of the guideline.
361-362	1	**Comment:** To abide by the 3Rs principle set out in Directive 2010/63/EU, we suggest changing the order of priority of animals used in dose determination studies. Specifically, we suggest prioritising naturally infected animals, if available, that might potentially benefit from the study instead of experimentally	Not accepted. The scope of the current revision was to align the guideline to Regulation (EU) 2019/6 and especially Article 4. While the comment is appreciated, any further in-depth amendments, especially pertaining new requirements, are not foreseen within this

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		inducing infections in additional animals, thereby reducing the total number of animals used. **Proposed change:** If no ~~experimental model is~~ naturally infected animals are available ~~and study conditions are well controlled~~, experimentally infected animals ~~naturally infected~~ ~~animals~~ can also be used as a last resort.	revision. However, the comment will be considered in the context of the next revision of the guideline.
584 **Section: 7.8 (Metaphylaxis)**	3	**Current Text:** "Metaphylaxis should be employed where infection is already present in part of the group and there is a high risk of spread to the rest." **Proposed change**: Add "Applicants **must** provide detailed evidence of the high risk of spread and demonstrate the failure of alternative infection control measures prior to metaphylaxis." This enhances accountability for metaphylaxis claims and strengthens the case for antimicrobial use only when absolutely necessary.	Not accepted. As outlined in section 7.8 'Special considerations for metaphylaxis claims', the use of antimicrobials for metaphylaxis is only permitted in the conditions laid down in Article 107(4) of Regulation (EU) 2019/6, *i.e.* when the risk of spread of an infection or of an infectious disease in a group of animals is high and where no appropriate alternatives are available. No changes to the guideline text are considered necessary.