18 October 2024
EMA/CVMP/EWP/44280/2024
Committee for Veterinary medicinal Products (CVMP)

Overview of comments received on '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)

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

Stakeholder no.	Name of organisation or individual
1	Access VetMed
2	AnimalhealthEurope
3	Cruelty Free Europe

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
2	AnimalhealthEurope welcomes this draft guidance indicating how the general flexibilities provided with Annex II can be applied to limited market veterinary medicinal products as defined by article 4 (29) of the regulation due to the characteristics of these products. Providing more clarity on data requirements and thus more predictability is crucial for developing this type of products. While the clear structure of the draft guidance is appreciated it has to be mentioned that there are several redundancies in the executive summary, the scope and the legal basis section. Please note that the Guideline would benefit from an additional note (introduction part) to clarify which non-immunological veterinary medicinal products could be in principle intended for limited markets but are by default excluded to be eligible for authorisation under Article 23 of Regulation (EU) 2019/6, explicitly antimicrobials and parasiticides. Reference is made to the Reflection paper on classification of a product as intended for a limited market according to Article 4(29) and/or eligibility for authorisation according to Article 23 (Applications for limited markets), EMA/CVMP/235292/2020 where it is stated: "For certain limited market products, including products that may be considered necessary to address an unmet medical need, adequate characterisation of safety and proof of efficacy is expected to be a basic requirement (for example, antimicrobials and parasiticides). Accordingly, such products may not be candidates for authorisation under Article 23.	Thank you for your comments. As the guideline specifically addresses data requirements to support efficacy and target animal safety for non-immunological VMPs already determined as not being eligible for authorisation under Article 23, it is not considered appropriate to include guidance on which products can/cannot be considered eligible for authorisation under Art 23. Determination of eligibility is a separate process (please see separate guidance entitled 'Requesting a limited market classification/confirmation of eligibility' and the CVMP 'Reflection paper on classification of a product as intended for a limited market according to Article 4(29) and/or eligibility for authorisation according to Article 23 (Applications for limited markets)').

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	Note that products intended to treat diseases that have zoonotic potential (for example, antimicrobials and parasiticides) will typically require adequate characterisation of safety and proof of efficacy as a basic requirement and may not be deemed eligible for authorisation in accordance with Article 23."	
3	Cruelty Free Europe welcomes the publication of this new guideline, which introduces clearer guidance on the circumstances under which the data requirements for limited market veterinary products can be reduced. However, the guideline does not explicitly state that reduced data requirements also come with the added benefit of reducing animal testing. In Europe there is a legal obligation to use alternatives to animal tests if available (i.e. Directive 2010/63) and to take the principles of the 3Rs into consideration – both of which should be clearly mentioned in the guideline (as they are in a similar separate draft guideline on 'safety and residue requirements for applications for non-immunological veterinary medicinal products intended for limited markets submitted under Article 23 of the Regulation (EU) 2019/16'). We urge the CVMP to reference legislation relating to the protection of animals used for scientific purposes, and to incorporate the principles of the 3Rs into the revised guideline where appropriate in the interests of animal welfare. This is in line with the goals set out in the EMA's published strategic reflection (https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf).	Thank you for your comments. Although reference is made to Directive 2010/63/EU and the 'Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches (EMA/CHMP/CVMP/JEG-3Rs/450091/2012)' in the references section, additional text has been introduced under the 'Legal basis' section to address your comments.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
73-81	3	**Comment**: In the 'Scope' section of the guideline it would be beneficial to note that the guideline also has a 3Rs benefit in offering reduced data requirements for limited market veterinary products. **Proposed change**: Add the following text to the end of this section. **"*This guideline also presents several opportunities to waive animal testing requirements for veterinary products intended for limited markets, which is in accordance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, Directive 2010/63/EU on protection of animals used for scientific purposes, and the 3R principles (replacement, reduction and refinement), and which should be applied to all testing involving animals.*"**	Partly accepted. Section 3 of the guideline has been updated to indicate that the 3Rs principles (replacement, reduction and refinement) should be applied when conducting studies on animals: '*In accordance with Annex II of Regulation (EU) 2019/6, all experiments on animals should be conducted taking into account the 3Rs principles (replacement, reduction and refinement) laid down in Directive 2010/63/EU on protection of animals used for scientific purposes*.'
82-92	3	**Comment**: Reference to Directive 2010/63/EC should be included in the 'Legal basis' section of the guideline. **Proposed change**:	Partly accepted. Although Directive 2010/63/EC does not represent a legal basis for this guideline per se, reference has been made in terms of applying the 3Rs principles.

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		Add the following test to the end of the Legal basis section (this is similar to the language that was used in previously adopted MUMS/limited market guidelines): **"*Directive 2010/63/EU on the protection of animals used for scientific purposes should also be considered in relation to the conduct of all testing involving animals. This Directive outlines the 3R principles of replacement, reduction and refinement, which should be taken into account whether the study is a pre-clinical study within the scope of Directive 2010/63/EU or a clinical field trial that is outside the scope*."**	
108	2	**Comments**: the requirement for a more comprehensive safety and efficacy data package for a major use, minor species product does not support innovation and availability of medicines in minor species. **Proposed change:** please re-evaluate if the proposed requirement is in line with the aims of Reg 2019/06.	Not accepted. The requirement is considered to be in line with Regulation (EU) 2019/6, as an application for a VMP intended for a limited market target species but not eligible for authorisation under Article 23 requires that the data package is compliant with Annex II.
108	2	**Comment:** the requirement for a "… ***more*** *comprehensive data package for efficacy and target animal safety* ..." is lacking the explicit reference. ('more' than?) **Proposed change:** please add as a reference (to 'more') the alleviations through 'flexibility' to Annex II, to clarify that it is not 'more' than (standard) Annex II requirements.	Accepted. Note that for all applications concerned by this guideline, the data package must be fully compliant with Annex II. The difference being highlighted in the line referenced relates to the fact that, in some instances, there may be less opportunity to apply the flexibilities mentioned previously. The guideline has been revised to clarify this aspect better.

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118-120	1	**Comments**: It would be useful to have more specific guidance about the requirements of using scientific literature to support the dossier. In this way, the number of SA would be reduced.	Not accepted. The text is considered appropriate as is. Furthermore, it is not considered possible to provide the specific guidance being sought outside of scientific advice procedures.
127	2	**Comment:** Sentence for new studies refers to "efficacy" of a product only. However, the scope of the guideline is "efficacy and target animal safety data." **Proposed change:** "*Where new studies are conducted by the applicant to support the efficacy* ***and target animal safety*** *of a product…*"	Accepted. The guideline has been updated accordingly.
129	2	**Comment:** the recommendation to conduct pharmacological, toxicological and pre-clinical safety studies in conformity with GLP should be in line with the EC delegated Regulation 2023/183 which amends Reg 2019/6 as regards the requirements of GLP compliance set out in Annex II to that Regulation. **Proposed change:** Please clarify that the GLP requirement applies only to preclinical safety studies, not to pharmacological, toxicological studies.	Not accepted. The text in the guideline is consistent with Section I.1.6 of Annex II to Regulation (EU) 2019/6 as amended by Regulation (EU) 2023/183: '*Pharmacological, toxicological, residue and pre-clinical safety studies shall be carried out in conformity with the provisions related to Good Laboratory Practice (GLP) laid down in Directives 2004/10/EC and 2004/9/EC of the European Parliament and of the Council*.'
142-144	2	**Comment:** If a study is adequately powered and controlled but statistical significance cannot be reached, e.g. unavailability of a sufficient number of animals with the disease, a clinically relevant change should be considered. **Proposed change:** "*It should be possible in all cases to demonstrate a benefit of treatment (either relative*	Not accepted. As a default, it is expected that any effect claimed to be attributable to the VMP under investigation should be statistically supported, i.e. a statistically significant effect in order to exclude the possibility that the effect occurred purely by chance. The guideline as currently worded does not preclude results from underpowered studies (those failing to

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		*to a control or, where appropriate, relative to pre-treatment/baseline data) that is **preferably** statistically significant **but at least clinically relevant**.*"	reach statistical significance) to be taken into consideration ("*However, the practical limitations of data collection for an infrequently occurring disease will be taken into consideration*"). Clinical relevance must be demonstrated in all cases.
159	2	**Comment:** To be aligned with the general requirements for scientific journals in line 118, requiring ideally peer reviewed journals, line 159 should be adapted as below. **Proposed change:** "*Data should be based on literature, e. g. **ideally** peer-reviewed articles*."	Not accepted. Since peer-reviewed articles are cited as an example, the word 'ideally' is not considered necessary. Moreover, this is stated in section 4, former line 118: '*Scientific literature, ideally from peer-reviewed journals* […]'.
201-227	3	**Comment**: We appreciate the minor changes that have been made to further clarify the conditions under which a target animal safety (TAS) test might not be required for limited market veterinary products. However, we would like to suggest some further strengthening of the language. The TAS has been criticised for being inhumane, wasteful and of limited scientific validity. For example, a 1996 review article highlighted that "there may be a significant number of drugs in which more target species animals may be destroyed during testing than would ever die from toxicity in clinical use" (A proposed design for conducting target animal safety studies for developing new veterinary pharmaceuticals. (1996). Regulatory Toxicology and Pharmacology, 23: 49-54).	Not accepted. A VICH-compliant TAS study conducted in healthy animals is a standard requirement for applications for veterinary medicinal products. With reference to the concern expressed about target animal species being 'destroyed', as indicated in VICH GL43, post-mortem examination may not be necessary in the absence of systemic clinical signs or abnormal findings in clinical pathology. Section 5.1.4 of the present guideline already foresees the possibility to utilise tolerance data from clinical trials as an alternative to a specific TAS study, provided the tolerance data generated from clinical trials is sufficiently comprehensive. Although toxicity data from laboratory animals in which tolerance is expected to be similar may be used to supplement tolerance data, it is not considered appropriate to restrict such data to only that

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		It also concluded that "the upper limit of safety is not a single-point dose for the entire population of target species, and so any attempt to indicate an absolute upper limit creates a false sense of security". Furthermore, since single dose toxicity studies in two species are already requested as a standard requirement for the safety testing of new veterinary medicines, it is not clear what added value the TAS could have to the overall safety assessment. We request that stronger recommendation to avoid this superfluous test be included in this section of the guideline. For example, by the insertion of text that was in the CVMP's draft version of the 'Guideline on efficacy and target animal safety data requirements for veterinary products intended for MUMS/limited market', 21 January 2016. **Proposed change**: "*Appropriate data should be provided to characterise local and systemic tolerance of the veterinary medicinal product in the target species following administration by the proposed route.* *The requirements for specific target animal safety studies of an application eligible for limited markets will depend on the information available on the safety of the active substance/product in the species eligible for limited markets and/or another species. This information may include* ***existing*** *data from toxicity studies in laboratory animals, literature reports,*	which is existing, i.e. prevent applicants from generating their own laboratory animal toxicity data if warranted. The second and third proposals are not accepted. 'Should be' allows more flexibility. The proposed text at the end of the paragraph is not in line with what is expected from the results of a target animal safety study, e.g. establishing a safe dose for further studies.

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		pharmacovigilance data, and safety information derived from efficacy studies. *In general, target animal safety (local and systemic)* ***is*** ***~~should be~~*** *confirmed in healthy animals of the target species in a negative-controlled target animal safety (TAS) study implemented under well-controlled laboratory conditions in line with the principles of VICH GL43 in order to characterise signs of intolerance and to establish an adequate margin of safety using the recommended route(s) of administration.* ***However, the benefit of conducting standard target animal safety studies in healthy animals is questionable because use of the product in healthy animals may not provide a reliable indication of the expected tolerance in the target population associated with normal field use of the product. A more suitable approach may be to investigate tolerance within the scope of field studies on efficacy.***"	
202	2	**Comment:** we suggest changing to local **and/or** as local tolerance would only concern certain type of route of administration and not always the case. **Proposed change:** "*…local and****/or****…*".	Partly accepted. The words 'local and systemic' have been deleted to avoid any misunderstandings.
209	2	**Comment:** we suggest changing to local **and/or** as local tolerance would only concern certain type of route of administration and not always the case.	Partly accepted. The words 'local and systemic' have been deleted to avoid any misunderstandings.

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		Proposed change: "*…local and**/or**…*".	
212	2	**Comment:** we suggest maintaining alignment with the purpose of the VICH GL43. **Proposed change:** "*…in order ~~to characterise signs of intolerance and~~ to establish an ~~adequate~~ margin of safety using the…*"	Not accepted. It is not understood why this text would not be in line with VICH GL43. Confirmation of margin of safety is only one aspect mentioned in the 'Objectives' section of VICH GL43. It is also mentioned that the purpose of VICH GL43 is the identification of target organs, which is considered to be reflected by the recommendation in the current guideline to characterise signs of intolerance.
214	2	**Comment:** Every substance may have safety concerns which are not consequential, thus the concerns should be described in more detail. **Proposed change:** "*For substances for which a **serious** safety concern exists, a target animal safety study in line with VICH GL43 is considered mandatory*."	Not accepted. There may be safety concerns which may not be serious but may still prove consequential. Thus, it is not supported to include 'serious' in the text.
216-218	1	**Comments**: Some guidance about what is considered negligible would be useful. Ideally, some examples or references to other guidelines could be given/mentioned.	Not accepted. This will be a case-by-case decision. The case of the product having negligible systemic exposure would need to be supported by the applicant.
230	2	**Comment:** Suggest to align the sentence in lines 229-230 with lines 136-137 and adapt line sentence in lines 230-231. **Proposed change:** "*Clinical trials should be conducted using the final formulation and carried out in accordance with established principles of good clinical practice, **unless otherwise justified**. Experimental*	Partly accepted. Text amended to include '*unless otherwise justified*' at the end of the first sentence. In the second sentence, *'if considered necessary*' is not accepted, since it does not correspond to '*unless otherwise justified*'.

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		data such as exploratory/pilot trials, or results from non-experimental approaches should be confirmed by clinical trials, ***if considered necessary***."	
End of Document - Annex	2	**Comment:** In analogy to MUMS GL or current reflection paper on classification a comparison TABLE would be helpful for better understanding of differences. **Proposed change:** Please insert a TABLE as Annex comparing: Current application of Limited Market flexibility under Annex II Reg 2019/6 vs. full Annex II under Reg 2019/6.	Not accepted. The flexibilities are outlined in the text and evaluated on a case-by-case basis. Even if a product meets the definition of 'limited market' in Article 4(29) the dossier would still be Annex II-compliant and a comprehensive set of safety and efficacy documentation in accordance with the requirements of Annex II of the Regulation will be required as stated in the guideline.