8 December 2016
EMA/CVMP/EWP/523421/2016
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on 'Guideline on efficacy and target animal safety data requirements for veterinary medicinal products intended for minor use or minor species (MUMS)/limited market' (EMA/CVMP/EWP/117899/2004–Rev.1)

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

Stakeholder no.	Name of organisation or individual
1	Asociación Estatal Empresarial de Medicamentos para la Salud Animal (ADIPREM)
2	European Group for Generic Veterinary Products (EGGVP)
3	European Coalition to End Animal Experiments (ECEAE)
4	IFAH Europe

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	Data for antimicrobial resistance: It should be enough with MICs literature data published. In case of lack of literature: studies with fewer strains (for example: maximum 10) should be accepted.	See comments below (line 178).
1	Clinical Study and Tolerance Study: A clinical efficacy trial should be enough also to assess tolerance.	See comments below (lines 229 and 245).
1	Pre-clinical data for minor species of already authorized for major species products should not be required. Extrapolation of the pre-clinical data of major species should be sufficient.	See comments below (line 212).
1	In point 6.1. Pre-Clinical Studies: (…) The proposed treatment regimen should be justified using: Specific dose determination studies, and/or Literature data/results of pilot studies/clinical experience reports, and/or Extrapolation from another species for which the product is authorized. PK / PD study should not be necessary.	See comments below (line 83).
2	EGGVP appreciates the opportunity to comment on this draft guideline and welcomes the revision of the MUMS / limited market guidelines. By definition, veterinary medicines intended for MUMS / limited market are of less interest for Industry. The current guidelines are very demanding in terms of studies workload and requirements, making the return of investment very lengthy. This problem is reinforced by EGGVP members' experiences.	Noted.
2	A general comment is that, in order to provide applicants with the necessary clarity and certainty, ambiguous terminology related to requirements (i.e. "may", "might"..) should be avoided as much as possible. Predictability is a determining factor for industry and data requirements and responsibilities should be more clearly defined. Several examples are provided under specific comments.	Text of the guideline has been reviewed in this regard.

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3	The ECEAE welcomes an update to this guideline, which now includes opportunities to reduce data requirements for veterinary medicines intended for MUMS/limited market, which in turn could result in the reduction of animal tests. However, nowhere in the guideline does it explicitly state that these changes come with the added benefit of saving animals. In Europe there is now 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 so as to further encourage their implementation. 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.	Text of the guideline has been reviewed in this regard.
4	IFAH-Europe welcomes the opportunity to comment the proposed new version of the guideline. It is with regret that we note that this revision is more restrictive in comparison to the previous version as some elements allowing justified deviation have been deleted. In our view, the new wording is a disincentive for the development of a product that would apply for a MUMS application since nearly the same requirements as for a major use are required. A discrepancy was detected between the more specific sections 6-7 and the general sections namely the introduction and section 5. In section 6-7 it is clearly stated that the applicability of reduced data requirements is always a case by case decision and that those should be scientifically justifiable; on the other hand possibilities for reduced data requirements are already limited for certain classes of products before an assessment is in place. This might reduce beneficial developments in the field of antimicrobials (line 84), products where	Noted.

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	resistance might occur (line 178 e.g. antimicrobials and antiparasitics) and GMO containing vaccines (line 84) among others without conducting a proper scientifically based assessment. In addition, when compared with the previous version of the guideline, we noticed the deletion of a complete paragraph, in Section 7 “Approval of veterinary medicinal product in exceptional circumstances”, that allowed a certain degree of interpretation and discussion with the required data. Now removed the industry sees little flexibility in the application of the guideline and the proposed revised guideline appears very similar to a full application significantly restricting the MUMS interest. If the reason for this was the rare use of this pathway more appropriate options for early access could be taken into consideration (e.g. conditional use).	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
29-41, Executive summary	3	**Comment**: we suggest that, as well as highlighting the main benefit of reducing regulatory requirements for veterinary medicines intended for MUMS/limited market (i.e. 'to stimulate the development of new veterinary medicines'), the positive implication of this on animal savings should be mentioned in the executive summary. This would also be an appropriate place to reference the 3Rs principles and highlight the legal obligation to conduct animal tests only as a last resort. **Proposed change**: Add: "This guideline also presents several opportunities to waive animal testing requirements for veterinary medicines intended for MUMS/limited market, which is in line with the recent implementation of Directive 2010/63/EC (regarding the protection of animals used for experimental and other scientific purposes) and the 3Rs principles of replacement, reduction and refinement".	Accepted.
78	4	**Comment:** Based on the intention to support product development in MUMS and to provide clear guidance under which circumstances data requirements can be reduced stronger wording should be proposed. **Proposed change:** Furthermore, the specific requirements will depend on the data and knowledge available, e.g. there ~~may~~ **will** be scope for reductions if a product has been authorised already for a major species or major use or an MRL has been established	Accepted.

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		for a major species, or if a product concerns an active substance belonging to a well-known class of substances.	
81	4	**Comment:** Based on the intention to support a more flexible approach for VMP indicated for animal species and indications representing smaller market sectors possibilities for data reductions should not be generally limited for new active substances, novel therapies or products first in class. **Proposed change:** However, for products containing entirely new active substances, novel therapy products or products representing first in class the possibilities for data reduction are ~~likely to be limited~~ **decided on a case by case basis**.	Accepted.
83-87	4	**Comment:** The proposed guideline states that the possibility for reducing data requirements for products presenting a specific risk is not possible. As examples antimicrobials in general and vaccines containing GMOs are mentioned. It should be clarified what exactly specifies these substances for imposing a specific risk compared to other substances. It is accepted that data requirements for an effective dosing regime for a certain disease might not be reduced. Nevertheless those requirements might still be reduced in regards to minor species if it can be proven that PK-PD relationship is similar to one already obtained in a major species. In general the possibility to grant incentives is still an option to support the development of, for example, effective antimicrobials and vaccines containing GMOs.	Partly accepted. It is not customary to refer to a concept paper in a published guideline. Moreover, incentives might change during the lifetime of the guideline while PK/PD concepts for extrapolation are not yet well known.

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		Otherwise treatment possibilities of important minor diseases and species might be neglected in the development, which is not within the scope of this guidance. **Proposed change:** Similarly, for some products ~~presenting a specific risk, e.g. for products containing an antimicrobial or vaccines containing GMOs,~~ the possibility for reducing data requirements will be ~~severely~~ limited in the area related to addressing a specific ~~the~~ risk, i.e. adequate data to justify the indication and establish the appropriate dosage regimen or data to ensure safe and efficacious use ~~of such a vaccine~~ will need to be established, even if the product is classified as MUMS/limited market. Nevertheless those products might be eligible for incentives and for an extrapolation via a valid PK-PD assessment for minor species (as already outlined in the 'Concept paper for the revision on the guideline for the 4 conduct of pharmacokinetic studies in target animal 5 species'.)	
84	4	**Comment:** References to vaccines within the current guideline may cause confusion as a specific guideline for immunological veterinary medicinal products exists. **Proposed change:** We suggest choosing alternative examples.	Accepted.
95	1	**Comment:** The general aim of this guideline is to define acceptable data requirements for the demonstration of efficacy and TAS for VMP for minor uses or minor species, **Proposed change:** therefore when an active	Accepted.

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		substance product has been authorised for the same or a similar indication in another target species, information relating to use in that species ~~may~~ **can** be used in support of the application.	
95	2	**Comment:** As in general comments **Proposed change:** therefore when an active substance product has been authorised for the same or a similar indication in another target species, information relating to use in that species ~~may~~ **can** be used in support of the application.	Accepted.
140-158, Legal basis	3	**Comment**: Reference to Directive 2010/63/EC should be included in the 'legal basis' section. **Proposed change**: Add: "This document should be read in conjunction with Directive 2010/63/EC (regarding the protection of animals used for experimental and other scientific purposes).	Accepted.
170-171	4	**Comment:** The expression 'more comprehensive data package' is very vague and should be clarified. **Proposed change:** '…where a more comprehensive data package for safety and efficacy as outlined in the following/ according to the following guidelines…'	Accepted.
174-177	4	**Comment:** Restriction of the MUMS application to an already known compound, this severely limits the ability for the applicant to develop a substance under conditional approval which constitutes a disincentive for the industry. **Proposed change:** Please replace the wording on these bullet points to reflect a discussion of	Partly accepted. A new sentence has been added to section 5 which advocates a case-by-case determination.

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		requirements on a case by case basis.	
178	4	**Comment:** According to the proposal a more comprehensive data package is warranted 'where there are special concerns (e.g. resistance)'. It is not clear, why a solid extrapolation of, for example, PK-data obtained in the MUMS species should not be applicable for extrapolating other data from major species to prove the safety and efficacy. The assessment if the reduced data package is sufficient should be solely scientifically based and justifiable (as outlined in line 161-163). If special data regarding the potential resistance is required it should not impact necessarily the data requirements for safety and efficacy in general but rather complement them. **Proposed change:** Please delete the bullet point: 'Where there are special concerns (e.g. resistance).' as this is already included in a sound scientific assessment of a reduced data package.	Partly accepted. Dose finding or PK studies in goats may be required because dose regimen cannot be extrapolated from bovine or ovine or there may be particular issues such as known resistance that merit special consideration.
180	4	**Comment:** Asking for appropriate data to characterise the mechanism of action might not be appropriate in the case of MUMS. In particular, for some parasites in minor species or limited markets the site of action of may not be known. The literature available should be submitted but no data should be required (as long as the efficacy of the product is shown in clinical studies). **Proposed change:** Please delete this requirement.	Accepted.
212-213	1	**Comment:** whenever scientifically justifiable interspecies extrapolation of pre-clinical data to support applications for minor species is accepted **Proposed change:** Thus the proposed treatment	Accepted.

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		regimen ~~may~~ **can** be justified	
212-213	2	**Comment:** As in general comments **Proposed change:** Thus the proposed treatment regimen ~~may~~ **can** be justified	Accepted.
229-233	3	**Comment**: The target animal safety test (TAST) has been criticised for being inhumane and wasteful and its scientific validity has also been questioned. For example, a 1996 review article highlighted the fact 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*). 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 TAST could have to the overall safety assessment. We request that stronger recommendation to waive this superfluous test be included in this section of the guideline (similar to what is recommended in lines 255-259 of the guideline for products for minor uses). **Proposed change**: "Where no/limited data on the safety profile of the active substance in the target	Partly accepted. The text of the section has been re-written to make it clearer.

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		species are available, a basic controlled study demonstrating the safety of the (near) final formulation in the target species **may** ~~will~~ be needed~~.~~ ~~In order to demonstrate a margin of safety in the target species, the study should be designed to investigate the tolerance to the product when administered at doses in excess of the recommended treatment dose~~. 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. Therefore, a more suitable approach may be to investigate tolerance within the scope of field studies on efficacy." 	
240	4	**Comment:** For some indications that cannot be treated with registered products the GL should give alternatives. **Proposed change:** Please add: " an uncontrolled field study may be acceptable, if justified"	Accepted.
244	1	**Comment:** If a field study has been provided and the selected dose is justified **Proposed change:** dose confirmation studies ~~**might**~~ **should** not be required	Accepted.
244	2	**Comment:** As in general comments **Proposed change:** dose confirmation studies ~~**might**~~ **will** not be required	Partly accepted. ('should' used in place of 'will')
245-248	1	**Comment:** Where the efficacy of the test product has been evaluated in the minor species in dose	Partly accepted.

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		determination and/or dose confirmation studies and where adequate data are available relating to TAS, **Proposed change:** field studies ~~**may**~~ **should** not be necessary. In such cases pharmacovigilance follow-up reports should be enough.	Section has been re-written to clarify requirements.
245-248	2	**Comment:** As in general comments. Possibility to use pharmacovigilance data in case that field studies are not considered necessary. **Proposed change:** Where the efficacy of the test product has been evaluated in the minor species in dose determination and/or dose confirmation studies and where adequate data are available relating to target animal safety, field studies ~~**may**~~ **will** not be necessary. In such cases, ~~the absence of field studies must be justified~~ pharmacovigilance data should be used as justification**.**	Partly accepted. Section has been re-written to clarify requirements.
253-254	3	**Comment**: Section 4 sets out the 'legal basis' of the guideline and does not detail any general requirements. We therefore assume that there is a typo in this sentence and that 'Section 6' was meant to be referenced instead. **Proposed change**: "Notwithstanding the case-by-case approach to establishing efficacy requirements for minor use indications, the general requirements as detailed in Section **6** ~~4~~ should be satisfied."	Partly accepted. This section has now been removed from the document.
255-259	1	**Comment:** For certain minor use products, in cases where the use of the product in healthy animals is questionable because it may not provide a reliable indication of the expected tolerance in the target population.	Partly accepted. This section has now been removed from the document.

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		Proposed change: Then tolerance ~~**should**~~ **must** be investigated within the scope of field studies on efficacy	
255-259	3	**Comment**: It is not clear why the recommendation to waive this cannot be broadened since the explanation given appears to be a universal one. **Proposed change**: "~~For certain minor use products (e.g. products for the treatment of endocrine disorders),~~ 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. ~~In such cases, tolerance should be~~ Therefore, a more suitable approach may be to investigate tolerance ~~investigated~~ within the scope of field studies on efficacy".	Partly accepted. This section has now been removed from the document.