8 December 2016
EMA/CVMP/QWP/472725/2016
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on 'Guideline on quality data requirements for veterinary medicinal products intended for minor use or minor species (MUMS)/limited market' (EMA/CVMP/QWP/128710/2004-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	IFAH Europe
2	Pestizid Aktions-Netzwerk e.V. (PAN Germany)
3	European Group for Generic Veterinary Products (EGGVP)
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1. General comments – overview

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
1	IFAH-Europe welcomes the opportunity to comment on this draft Guideline. Please find a few comments below.	See below.
2	The guideline is intended to reduce data requirements where possible for products classified as MUMS/limited market while still providing assurance of appropriate quality safety and efficacy and complying with the legislation in place and leading to an overall positive risk-benefit balance for the product. In the view of PAN Germany the guidelines must ensure that reduced data requirements for MUMS/limited market are not asserted at the expense of reduced environmental protection. The VICH-guidelines that govern the content and scope of the environmental impact assessment have been in force only since 2005. (www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004386.pdf). Previously authorised medicinal products haven't been tested for their environmental impact according to those guidelines. In consequence about 2/3 of the veterinary medicinal products in use are so called "old products" which have never been tested for their environmental impacts. The Guidelines must ensure that a complete ERA had been carried out before extending the authorisation for MUMS/limited markets. Further spreading of antibiotic resistances must be prevented especially when the market authorisations of existing veterinary or	Comments on environmental impact are not relevant to the Quality guideline, but are noted. See below regarding specific comments.

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	human medical products are extended for MUMS/limited markets. Critically important antimicrobials authorised as human medical products should be excluded from the extension for veterinary use in minor species. Water and aquatic ecosystems are especially endangered by pollution from veterinary medical products. Pharmaceutical residues in water pose already an environmental problem and a problem (technically and economically) to Water suppliers. Growing fish in aquacultures is an expanding business while the number of authorised medical products for food-producing aquatic species is limited. It can be expected that an increased use of veterinary medicinal products authorised for use in terrestrial animals leads to increased environmental pollution when used for MUMS in open aquaculture systems with no specific waste water treatment facilities. The extension of an existing veterinary medical product authorised for the use in terrestrial animals for a minor aquatic specie must therefore be particularly strictly reviewed. Without a complete ERA adapted to the environmental and use conditions of the minor specie an extension of the authorisation should be denied.	
3	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.	See below.
3	The proposed Guideline is straight forward and the requirements are	See below.

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	clear. EGGVP generally supports the detailed quality guidance for MUMS and agrees with its content. Some important aspects are detailed below for consideration.	
4	In addition to the general comments from AVC which is very pleased to have the opportunity to comment on this new GL., I want to make a specific comment on the GL Quality, which I had no time to share with the colleagues of AVC of our WP MUMS, of which I am the chairman Yes, it is a follow up of all the efforts already made by EMA and more specifically CVMP on this topic	See below.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Middle line 81 till 83	4	**Comment**: It is mentioned that specific requirements will not be needed for "products containing entirely new active substances…". In fact a general opportunity which occurs often is that the applicant wants to register as anti-parasitic VMP a product which is already used as a pesticide, insecticide for plants. Some substances are already covered by the REACH procedures; but are considered as VMP when they are applied in animals for prevention or treatment of a disease. **Proposed change**: Add a sentence "Sometimes the applicant wants to register as VMP a substance already registered in another field: eg products covered by the REACH regulations."	Not accepted. The text on pages 81 till 83 is that agreed by CVMP and is the same for all MUMS guidelines. Furthermore, a substance already registered in another field is unlikely to possess a suitable data package and data would in any case have to be provided. The text mentioned is in the Introduction and the proposed addition does not seem to add much.
88-89	1	**Comment:** The guideline is very clear on possible reduction of requirements in cases 5.1, 5.2 and 5.3. However, lines 88 and 89 very strongly recommend having confirmation of the data package necessary via scientific advice. Having to perform a scientific advice for clarification of quality requirements for all MUMS applications would highly increase the workload of the applicant, it is not felt as justified and would reduce the value of the guideline to industry. A scientific advice procedure is always open for the applicant, therefore, it is suggested that the specific advice of applying for a scientific advice is limited to cases 5.4.	Not fully accepted. The text on pages 89/90 is that agreed by CVMP and is the same for all MUMS guidelines. Furthermore, the text states that applicants are advised to request scientific advice. It will not be mandatory to request scientific advice. However, the text could be revised to state: "The guidance provided in this document is general. Applicants ~~should consider requesting~~ are reminded that the S~~s~~cientific A~~a~~dvice procedure is available ~~on their individual~~

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		Proposed change: Please modify the text on lines 88/89 to read: "The guidance provided in this document is general. **In such cases,** applicants are advised to request scientific advice on their individual data package to confirm the precise requirements for their specific application."	~~data package~~ to confirm ~~the~~ precise requirements for ~~their~~ a specific application."
117	2	**Comment**: We propose to ad trout as a major specie. Only salmon is considered to be a major specie. But looking at the Top 10 species in aquaculture in the European Union (2013) trout is number two regarding its value (value in thousands of EUR and percentage of total) and the produced volume (volume in tonnes live weight and percentage of total) is even bigger that for salmon (see http://ec.europa.eu/fisheries/documentation/publications/pcp_en.pdf Page 28). In 14 member states (MS) trout production plays a major role and in BE, BG, DK; DE, EE, AT, SK, FI, SE and SI trout is the number one main species in aquaculture (see http://ec.europa.eu/fisheries/documentation/publications/pcp_en.pdf Page 29/30). Trout therefore should be added to the list of major species. **Proposed change**: salmon ***and trout***	Not accepted. This comment is not relevant to the Quality MUMS Guideline. The species are specified in the two guidance documents listed below, the first being the pivotal one regarding the species: • Revised Policy for classification and incentives for veterinary medicinal products indicated for minor use minor species (MUMS)/limited market (EMA/308411/2014) http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2014/09/WC500172928.pdf • Guidance on the classification of veterinary medicinal products indicated for minor use minor species (MUMS) / limited market (EMA/CVMP/388694/2014) - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/12/WC500179577.pdf
121-122	2	**Comment**: Especially in aquaculture production and consumption patterns might change swiftly. A specie that does not play a major role today may play such in the near future. Therefore the list of major species should be revised and updated regularly (following a	Not accepted. This comment is not relevant to the Quality MUMS Guideline. The species are specified in the two guidance documents listed below, the first being the pivotal one regarding the

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		fixed time interval).	species: • Revised Policy for classification and incentives for veterinary medicinal products indicated for minor use minor species (MUMS)/limited market (EMA/308411/2014) http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2014/09/WC500172928.pdf • Guidance on the classification of veterinary medicinal products indicated for minor use minor species (MUMS) / limited market (EMA/CVMP/388694/2014) - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/12/WC500179577.pdf
155 -160	1	**Comment:** Lines 156 and 227-229 introduce a new requirement to variations adding a new target species, i.e. confirmation that the already authorised part II dossier reflects the current applied methods for manufacture, control and testing of the product. This requirement seems to be redundant for variation applications as in a variation it is understood that only the documentation that is being changed is submitted and all other dossier parts remain valid and reflects the current applied methods for manufacture control and testing. **Proposed change:** Please amend the text to read: "However, it will be necessary to submit a supplement to the part II dossier that confirms that the already authorised part II dossier ~~**reflects the currently applied methods for manufacture, control and**~~	Not accepted. This requirement was consciously added to bring this section in line with the other sections of Part 5. The provision of the supplement is not resource intensive as it only requires a confirmation that the already authorised Part II dossier reflects the currently applied methods, which it should, as the product would not otherwise be in accordance with its MA. As stated by IFAH-Europe, all other dossier parts remain valid and reflect the current applied methods for manufacture control and testing.

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		~~**testing of the (157) product and b)**~~ considers the practical use of the medicine in the minor species, to establish if accurate dosing of the product can be achieved and to ascertain if the integrity of the product might be compromised by a modified pattern of use."	
155-162	3	**Comment**: it makes no sense to confirm in a supplement the currently applied methods for manufacture, control and testing, since this is supposed it is updated. One thing is part II of product that should be updated, and the other one is the inclusion for a minor specie or minor use or limited market.	Not accepted. It is important that no changes are made disguised as part of the MUMS application.
165-168	3	**Proposed change**: Additional homogeneity and stability studies may be required, unless it can be ~~demonstrated that the existing data are relevant~~ **justified that no additional homogeneity and stability studies are needed**.	Not accepted. The existing wording is preferred.
201- 208 278- 287	1	**Comment:** Under § 5.1 and 5.3, addition of paragraph "* on process development and validation data…" It reads: "For standard and *non-standard* processes, provision of a process validation scheme only." But "*Process development and validation data should be included in the dossier pre-authorisation as necessary in accordance with the normal requirements set out in the guideline on process validation." Guideline EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1 states under § 5.1 (Process validation, traditional approach): "…it is considered necessary to provide	Accepted. The paragraph covered by the asterisk in the draft guideline seems to negate the meaning of the previous paragraph. Amended throughout the guideline.

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		production scale validation data in the marketing authorisation dossier at the time of regulatory submission, for example… where the applicant is proposing a *non-standard* method of manufacture…" Industry welcomes the reduction of requirement for non-standard processes, however, when the (*) refers again to the specific requirements of the validation guideline, it is may be understood that data reduction may not apply to non-standard processes. It is also noted that reference to the specific guideline may be redundant as the following sentence is already included in line 105. "As a general principle, the CVMP, joint CVMP/CHMP and VICH guidelines concerning quality are applicable to minor use/minor species products." **Proposed change:** Please delete the following text " ~~*** Process development and validation data should be included in the dossier pre-authorisation as necessary in accordance with the normal requirements set out in the guideline on process validation.**~~"	
210	3	**Proposed change**: Data for 2 ~~pilot~~ batches ~~only~~: **1 pilot batch and second batch may be smaller**	Accepted for standard processes, but clarified further to state "~~D~~For standard processes, data ~~required for 2 pilot batches only~~ for 1 batch of at least pilot scale and a second batch which may be smaller.". For non-standard processes, where there is no process

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			validation 2 batches of at least pilot scale are needed so the following added "For non-standard processes data for 2 batches of at least pilot scale." Wording clarified throughout the guideline.
215	3	**Comment**: In some cases requirements for new stability data studies could be relaxed or even not required. The quality of the product has been demonstrated in first authorisation in cases like inclusion of minor specie or minor use. Ongoing stability one would be applied in case of new packaging included. Not always a new packaging would mean more stability risk, and then a possible justification would be accepted. **Proposed change**: Data required in application for two ~~pilot~~ batches only: **1 pilot batch and second batch may be smaller. Applicant may not submit new stability data if appropriately justified.**	Not fully accepted. The draft already states that cross-reference to the existing Part II will be allowed where applicable, therefore the statement "Applicant may not submit new stability data is appropriately justified" is not supported. However, this is a line extension for an existing active substance where the usual requirement is for 2 pilot batches with possibly a third smaller, a relaxation to 1 pilot batch and a second smaller seems reasonable. Wording therefore amended to "Data required in application for 1 ~~pilot~~ batch of at least pilot scale and a second batch which may be smaller ~~two pilot batches only~~."
214-223	1	**Comment:** Under § 5.1, the reference to bracketing/matrixing has been removed compared to previous guideline and compared to § 5.4 (line 330). The removal of this reference might be misinterpreted as such option is not acceptable which is not the aim we believe. **Proposed change:** The possibility of applying bracketing/matrixing should be kept.	Accepted. In this situation, where line extensions are necessary to introduce a different strength, the possibility of applying bracketing/matrixing should be included. Reference reintroduced.

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227-229	1	**Comment:** see also lines 155-160 above. These lines introduce a new requirement to variations adding a new target species. **Proposed change:** Please delete the text "~~**A supplement to the part II dossier confirming that the already authorised part II dossier reflects the currently 228 applied methods for manufacture, control and testing of the product should be supplied**~~". (part of line 227 and lines 228-229).	Not accepted. See lines 155–160 above.
226-229	3	**Comment**: This requirement for additional supplement should be removed as dossiers are updated and no confirmation for manufacturing methods and control testing are needed. I do not really understand the purpose to this additional supplement. **Proposed change**: In the majority of such cases the dosage rate and route of administration for the proposed minor use indication will be unchanged and therefore no additional Quality data would be required. ~~A supplement to the part II dossier confirming that the already authorised part II dossier reflects the currently applied methods for manufacture, control and testing of the product should be supplied.~~	Not accepted. This requirement was consciously added to bring this section in line with the other sections of Part 5. The provision of the supplement is not resource intensive as it only requires a confirmation that the already authorised Part II dossier reflects the currently-applied methods, which it should as the product would not otherwise be in accordance with its MA.
296-312	4	**Comment**: as mentioned above (see comment on line 81 to 83) in some entirely new medicine for use in MUMS, the active substance in such medicines are likely to be substances already used as pesticides.	Clarified. There may have been a misunderstanding with the original wording.

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		Typical example is oxalic acid against varroase in bees. It is mentioned (line 301-302) “in such cases, a full supporting quality data package will be required. And “applicants are advised to routinely request Scientific Advice for such applications” As example of areas in which the data requirements might be reduced reference is made in line 308 to “ for all active substances (ie pharmacopoeial and non-pharmacopoeial) formal stability studies…are not required….”. It is the first time that reference is made to the possibility to register for VMP for MUMS non-pharmacopoeial active substances. AVC members have been confronted with development of dossiers in which the applicant proposed a non- pharmacopoeial active substance(and this mainly for financial reasons) and it was rejected by the reference member state in the early discussions; based on the principle that only pharmacopoeial active substance can be used in VMP. Can the CVMP not consider this case by case and not rejected it automatically? **Proposed change**: add before line 305 “Active substance quality: Non-pharmacopoeial active substances are normally not allowed in VMP; but under some circumstances, and case by case, the quality data submitted by the applicant for a non pharmacopoeial active substance should be evaluated as a potential candidate for an active substance of a VMP for MUMS.”	Non-pharmacopoeial active substances are allowed in VMPs. Many VMPs containing non-pharmacopoeial active substances are authorised in the EU. Therefore, for clarification the following sentence has been added: “Where an active substance is monographed in the Ph. Eur. or in the pharmacopoeia of an EU member state, the use of a non-pharmacopoeial grade is not acceptable.”