18 October 2024
EMA/CVMP/QWP/50888/2024
Committee for Veterinary Medicinal Products (CVMP)

Overview of comments received on 'Guideline on quality data requirements for applications for veterinary medicinal products other than biologicals intended for limited markets' (EMA/CVMP/QWP/47285/2022)

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

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	Once again, Access VetMed appreciate the opportunity to comment on this proposed/draft Guidance. In particular, as quoted in the previous guideline EMA/CVMP/QWP/128710/2004-Rev.1 (now superseded), Access VetMed value the possibility to refer to an authorised human medicine to waive the assessment of the Quality part for a Veterinary Medicinal Product application. Please kindly refer to the next page for specific comments/remarks on the text.	
2	AnimalhealthEurope would like to thank the CVMP for this Guideline and is grateful for the opportunity to comment. Please find some comments below. Should you have further questions, AnimalhealthEurope is happy to provide any clarification needed. Reference to Article 23 in this guideline is confusing since the scope of the guideline is all products that meet the definition of limited market in Article 4(29), including both applications eligible and not eligible under Article 23. Article 23 addresses safety and efficacy documentation and does not differentiate with regard to quality data requirements. The legal basis for this guideline on quality data requirements would consequently be expected not include Article 23. Unless justified, it is proposed to retain all elements of the previous MUMS guidance of December 2016 - EMA/CVMP/QWP/128710/2004-Rev.1 – "Guideline on quality data requirements for veterinary	<u>Reference to Article 23</u> The point is accepted and reference to Article 23 is removed from the legal basis. <u>Retention all elements of the previous MUMS guidance of December 2016</u> These elements are addressed individually in the comments below.

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	medicinal products intended for minor use or minor species (MUMS)/limited market". In general, the requirements for limited market applications have increased compared to MUMS guidance EMA/CVMP/QWP/128710/2004-Rev.1. As an example, it used to be possible to submit only a process validation scheme for non-standard processes but is not under the proposed guideline. On the other hand, it is very much appreciated that photostability data are not required if the product is stored in a light-impermeable outer packaging.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
54-56	2	Comments: We suggest specifying in lines 54-56 that the purpose of this guidance is limited to quality data. Proposed change: Please amend the text to read: "The purpose of this scientific guidance is to indicate how the general flexibilities provided within Annex II **for quality data** 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."	Accepted. Whilst it is explicit in the title of the document, that it is limited to quality data, there is no objection to including the text.
64-65	2	Comments: The reference to Article 23 in lines 64-65 is confusing since the scope of the guideline is all products that meet the definition of limited market in Article 4(29), including both applications eligible and not eligible under Article 23. Article 23 does not differentiate with regard to quality data and is therefore not considered relevant as a reference in this guideline. However, article 4(29) should be added as reference. Proposed change: Please modify the text to read: "The guideline should be read in conjunction with Regulation (EU) 2019/6, in particular **Article 4(29),** Article 8, ~~**Article 23**~~ and Annex II."	Accepted.

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73-76	2	"*Where a medicine is already authorised in the EU, a satisfactory set of supporting quality data already exist for the product and whilst this data need not be re-assessed in those Member States where the existing product is authorised, it should be provided with the application for the limited market product*." Comments: The above sentence leaves the door open to reassessment of existing quality data in those Member States where the medicine was not initially authorised, but where the applicant may seek registration of the new limited market product. To apply the principle of mutual recognition, limit administrative burden (one of the main objectives of Regulation 2019/6) and be consistent with the statement on line 103 that "Item 4 will not be assessed.", the following rewording is proposed: Proposed change: New wording: "*Where a medicine is already authorised in the EU, a satisfactory set of supporting quality data already exist for the product and whilst this data need not be re-assessed* ***~~in those Member States where the existing product is authorised~~***, *it should be provided with the application for the limited market product*."	Not Accepted. Where the existing product is not authorised in a MS, the MS should be able to review the data and raise issues, if required. This is the case for all marketing authorisation procedures, including MRP and SRP. A corresponding correction has also been made in section 4.1.1.
87	2	Comments: The footnote states that this item will not be assessed. However, compiling a full copy of the	Not accepted. ICH Q12 is not applicable to veterinary products. Furthermore, the concept of established conditions can only

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		approved dossier (including all the supporting documents like Certificates of Analysis), involves quite a lot of administrative effort. It is proposed to clarify that those dossier sections that ICH Q12 identifies to contain "established conditions" need to be submitted, but that those sections ICH Q12 considers supportive are not required.	be applied to dossiers that have been approved with identified established conditions. It cannot be applied retrospectively to old dossiers.
88-89	1	Comment: Access VetMed do not consider this point as relevant. According to Annex II of Regulation 2019/6: '*Documentation shall be supplied to demonstrate that materials originating from animal species relevant for the transmission of transmissible spongiform encephalopathies (TSE) comply with the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products, as well as with the corresponding monograph of the European Pharmacopoeia*'. The above point has no relation/link to use of products in species susceptible to TSEs. Proposed change: ~~5. An additional TSE risk assessment if the limited market product is to be used in a species susceptible to TSEs.~~	Not accepted. Compliance with the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products, is based on a risk assessment. One of the factors to be considered in this risk assessment is the presence of a species barrier. Therefore, if the product is to be newly used in a species susceptible to TSE, an updated TSE risk assessment is relevant.
122	2	Comments:	Accepted.

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		It is proposed to uphold the requirements as mentioned in the MUMS guidance of December 2016 - EMA/CVMP/QWP/128710/2004-Rev.1 – "Guideline on quality data requirements for veterinary medicinal products intended for minor use or minor species (MUMS)/limited market ": Under the section discussing multidose presentations, please insert the following after the sentence "In exceptional circumstances, for example for a sterile injection where the required dose volume cannot be measured, even with an insulin syringe, it might be necessary to develop and register with appropriate supporting quality data a lower concentration of the existing formulation." An alternative strategy that may be appropriate for non-sterile products is to supply or recommend an appropriate diluent. Data would need to be included in the part II supplement in order to demonstrate that the proposed diluent is suitable.	Some minor editorial amendments have been made to the proposed text to clarify that dilution would only be relevant for liquid dosage forms and to clarify where in the dossier the information should be located. The same text has been added to section 4.2, where the same strategy would also be acceptable.
139-143	2	"Final product process validation data - For standard processes, a process validation scheme and evaluation/validation data for critical parameters on at least 1 pilot scale batch should be provided. " Comments: For standard and non-standard processes, provision of a process validation scheme only would be sufficient. Thus, permitting process validation studies	Not accepted. Annex II, II.2.B (e) requires 'experimental studies validating the manufacturing process and, where appropriate, a process validation scheme for production scale batches;' The text '*and evaluation/validation data for critical parameters on at least 1 pilot scale batch should be provided'* is considered the minimum level of data that could be considered to fulfil the requirement to provide

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		to be conducted on full scale batches post authorisation. The final reports from such process validation studies are to be available for scrutiny during GMP inspections. However, the competent authority(ies) must be informed if problems are encountered on validation of the process at the full scale, together with the proposed action. Proposed change: It is proposed to uphold the requirements as mentioned in the MUMs guidance of December 2016 - EMA/CVMP/QWP/128710/2004-Rev.1 – "Guideline on quality data requirements for veterinary medicinal products intended for minor use or minor species (MUMS)/limited market ".	'*experimental studies validating the manufacturing process'* for a LM product.
140-141	1	Comment: Access VetMed kindly suggest that 'and' is replaced by 'or'. The process validation scheme is sufficient for the regulatory submissions according to EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1, Corr.1. Proposed change: For standard processes, a process validation scheme ~~and~~ **or** evaluation/validation data for critical parameters on at least 1 pilot scale batch should be provided.	Not accepted. As above. Annex II, II.2.B (e) requires 'experimental studies validating the manufacturing process and, where appropriate, a process validation scheme for production scale batches;' The text '*and evaluation/validation data for critical parameters on at least 1 pilot scale batch should be provided'* is considered the minimum level of data that could be considered to fulfil the requirement to provide '*experimental studies validating the manufacturing process'* for a LM product.

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140 – 141 197 – 198 227 – 228	2	Comments: For standard processes, neither Annex II to the NVR nor EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1, Corr.1 ask for "evaluation/validation for critical parameters on at least 1 pilot scale batch". The Pharmaceutical Development dossier sections would include data to support the critical steps, but there is no requirement that these data be generated on pilot scale. It therefore seems excessive to request this for limited market products, especially as it is not a requirement under EMA/CVMP/QWP/128710/2004-Rev.1. Proposed change: Therefore, for the reasons above, this requirement should be deleted.	Not accepted. Regulation 2021/805, section II.2.B (e) requires 'experimental studies validating the manufacturing process and, where appropriate, a process validation scheme for production scale batches;' The text '*and evaluation/validation data for critical parameters on at least 1 pilot scale batch should be provided'* is considered the minimum level of data that could be considered to fulfil the requirement to provide '*experimental studies validating the manufacturing process'* for a LM product.
142-143	1	Comment: No extra reduction is currently suggested for non-standard processes. EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1, Corr.1 states an equivalent wording: *'Data on a minimum of 3 production scale batches should be submitted unless otherwise justified. Data on 1 or 2 production scale batches may suffice where these are supported by pilot scale batches and a justification as highlighted above.'* Additional reliefs could be suggested, for example, acceptance of validation data on 2 pilot scale batches.	Not accepted. For non-standard processes, the absence of data on any full scale batches is not considered appropriate as non-standard processes are more likely to be impacted by scale up and pilot scale data will not necessarily be representative.

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		Proposed change: For non-standard processes, validation data on **2 pilot scale batches** ~~1 full scale batch~~ would be acceptable~~ if supported by validation data on 2 pilot scale batches~~.	
146-147 233-234	2	Comments: The requirement to provide batch analysis data for each finished product manufacturing site is rather difficult to meet for a product with limited market and is in addition to the requirements in Annex II to Regulation 2019/6. Proposed change: For the reasons above, it is proposed to delete this requirement.	Not accepted. Provision of site specific batch data is in accordance with the requirements of Regulation 2021/805 which states in section II.2.E5 '*In order to ensure the quality of the product is consistent from batch to batch and to demonstrate conformity with the specification, batch data shall be provided giving the results for all tests performed in general on [3]* ***batches manufactured at the proposed manufacturing site(s)*** *according to the described production process.'*
149	2	Final product stability Comments: It is proposed to uphold the requirements as mentioned in the MUMS guidance of December 2016 - EMA/CVMP/QWP/128710/2004-Rev.1 – "Guideline on quality data requirements for veterinary medicinal products intended for minor use or minor species (MUMS)/limited market ": Proposed change: Replace proposed sentence "Data for 2 batches of at least pilot scale. "by "Data **required in the**	Accepted.

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		application for 1 batch of at least pilot scale and a second batch which may be smaller."	
163-168	2	Comments: The wording of this paragraph is prone to misunderstandings. It first states that submission of "all the data in the aforementioned sections are not necessary" – but then goes on to explain that actually, only 4 items from section 4.1.1 are not required – everything else appears to be required. Proposed change: Clarification would be appreciated.	Partly accepted. The interpretation in the comment is correct. The text has been amended for clarity. '*in those cases information detailed in section 4.1.1 items 5-9 should be provided. Items 1-4 are not required to be provided.'*
185-186	1	Comment: Same comment as for lines 88-89 Proposed change: ~~5. An additional TSE risk assessment if the limited market product is to be used in a species susceptible to TSEs.~~	Not accepted. Compliance with the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products, is based on a risk assessment. One of the factors to be considered in this risk assessment is the presence of a species barrier. Therefore, if the product is to be newly used in a species susceptible to TSE, an updated TSE risk assessment is relevant.
197-198	1	Comment: Same comment as for lines 140-141 Proposed change:	Not accepted. Annex II, II.2.B (e) requires 'experimental studies validating the manufacturing process and, where appropriate, a process validation scheme for production scale batches;'

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		…, a process validation scheme and or evaluation/validation data for critical parameters on at least 1 pilot scale batch should be provided.	The text *'and evaluation/validation data for critical parameters on at least 1 pilot scale batch should be provided'* is considered the minimum level of data that could be considered to fulfil the requirement to provide '*experimental studies validating the manufacturing process'* for a LM product.
198-200	1	Comment: Same comment applies as for lines 142-143 Proposed change: For non-standard processes, validation data on **2 pilot scale batches** ~~1 full scale batch~~ would be acceptable ~~if supported by validation data on 2 pilot scale batches~~.	Not accepted. For non-standard processes, the absence of data on any full scale batches is not considered appropriate as non-standard processes are more likely to be impacted by scale up and pilot scale data will not necessarily be representative.
208-211	2	Comments: It is proposed that when the limited market MA is granted on the basis of an approved human medicines marketing authorisation quality data, change approved to quality data of the human medicine which are shown not to be in relation with the use as a veterinary limited market product should be automatically recognised without the need for a dedicated variation to the veterinary limited market authorisation. Only changes impacting items 5 to 10 (as mentioned under section 4.2 of the draft guideline) should be subject to review and assessment. An annual list of such changes impacting the human medicine quality dosser will contribute to	Not accepted. Variations to Part II of the dossier will be subject to approval by way of variation in the normal way. The text '*Following approval, variations to the authorised limited market product, with supporting data should be submitted in accordance with legislation for veterinary medicinal products.'* Is considered to adequately address this point.

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		reducing administrative burden without compromising the safe use of the veterinary limited market product.	
225	2	Comments: It is proposed to uphold the requirements as mentioned in the MUMS guidance of December 2016 - EMA/CVMP/QWP/128710/2004-Rev.1 – "Guideline on quality data requirements for veterinary medicinal products intended for minor use or minor species (MUMS)/limited market". Proposed change: Please insert the following: *Active substance stability:* **• For all active substances (i.e. pharmacopoeial and non-pharmacopoeial) formal stability studies according to CVMP guidelines are not required if testing to full specification immediately before manufacture of the final product is proposed. However, there might still be a need for some stress testing to investigate the degradation profile of non-pharmacopoeial substances and to check the stability-indicating characteristics of the control method.**	Noted. However, it is not necessary to include the text in the GL because it's applicable to all VMPs.
226-230	2	Comments: It is proposed to uphold the requirements as mentioned in the MUMs guidance of December 2016 - EMA/CVMP/QWP/128710/2004-Rev.1 – "Guideline on	Not accepted. Annex II, II.2.B (e) requires 'experimental studies validating the manufacturing process and, where appropriate, a process validation scheme for production scale batches;'

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		quality data requirements for veterinary medicinal products intended for minor use or minor species (MUMS)/limited market". *Final product process validation data: replace current proposal by:* • **For standard and non-standard processes, for full scale batches, provision of a process validation scheme only. Thus, permitting process validation studies to be conducted on full scale batches post authorisation. Final reports from such process validation studies are to be available for scrutiny during GMP inspections. However, the competent authority(ies) must be informed if problems are encountered on validation of the process at the full scale, together with the proposed action.**	The text '*and evaluation/validation data for critical parameters on at least 1 pilot scale batch should be provided'* is considered the minimum level of data that could be considered to fulfil the requirement to provide '*experimental studies validating the manufacturing process'* for a LM product. For non-standard processes, the absence of data on any full scale batches is not considered appropriate as non-standard processes are more likely to be impacted by scale up and pilot scale data will not necessarily be representative.
227-228	1	Comment: Same comment as for lines 140-141. Proposed change: For standard processes, a process validation scheme ~~and~~ **or** evaluation/validation data for critical parameters on at least 1 pilot scale batch should be provided.	Not accepted. Annex II, II.2.B (e) requires 'experimental studies validating the manufacturing process and, where appropriate, a process validation scheme for production scale batches;' The text '*and evaluation/validation data for critical parameters on at least 1 pilot scale batch should be provided'* is considered the minimum level of data that could be considered to fulfil the requirement to provide '*experimental studies validating the manufacturing process'* for a LM product.

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229-230	1	Comment: Same comment applies as for lines 142-143 Proposed change: For non-standard processes, validation data on **2 pilot scale batches** ~~1 full scale batch~~ would be acceptable~~ if supported by validation data on 2 pilot scale batches~~.	Not accepted. For non-standard processes, the absence of data on any full scale batches is not considered appropriate as non-standard processes are more likely to be impacted by scale up and pilot scale data will not necessarily be representative.
251-260	2	Comments: Refer to the comments to lines 64-65 above. The definitions in lines 251-260 are not considered relevant for this guideline and should be deleted. Proposed change: Please delete definitions in lines 251-260.	Accepted.
266-274	2	Comments: Refer to the comments to lines 64-65 above. The references in lines 266-274 are not considered relevant for this guideline and should be deleted. Proposed change: Please delete references in lines 266-274.	Partially Accepted. Reference to the concept paper is not deleted since it is the concept paper for the development of this guideline.