EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 October 2024
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Committee for Veterinary Medicinal Products (CVMP)

Overview of comments received on Guideline on quality data requirements for applications for biological veterinary medicinal products intended for limited markets (EMA/CVMP/IWP/228730/2022)

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

Stakeholder no.	Name of organisation or individual
1	AnimalhealthEurope

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
1	AnimalhealthEurope welcomes this proposal allowing some flexibility for the quality requirements for biological veterinary medicinal products intended for the 'limited-market'. We understood that all products which are under the scope of article 4(29) of Regulation 2019/6, will benefit from this guideline. Some specific references are made to this point in the following section detailing the more specific comments and change proposals.	Noted.
1	The flexibility as given as definition in this GL is general, leaves place for "case-by-case" interpretation. More complex quality requirements seem to be subject of Scientific Advice discussions. Although this scientific guideline does not address procedural points, it should be noted that the absence of fee incentives for products under limited markets, but not eligible to Art.23 (including for scientific advice request) is considered as a limiting factor and contradictory with the aim of enhancing availability of veterinary medicinal products, including for limited markets.	Noted. Fees are not part of the guideline.

2. Specific comments on text

Line number(s) the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome (if applicable)
Lines 37-39	1	**Comment:** We recommend that there is a clearer statement that this guideline applies for ALL 'limited-market' biological products, whether or not they meet the prescriptions of article 23. **Proposed change**: The general aim of this guidance is to define acceptable data requirements for the demonstration of the quality of biological veterinary medicinal products, including immunological veterinary medicinal (IVMPs) products classified as limited markets in line with Article 4(29) of Regulation (EU) 2019/6**, whether they meet the requirements of Article 23, or not.**	Accepted. Slightly reworded. Added for clarification.
Lines 60-62	1	**Comment:** We suggest specifying in line 60-62 that the purpose of this guidance is limited to quality data. **Proposed change**: 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. Added for clarification.
Lines 66-67	1	**Comment:** We suggest clarifying the scope by aligning the description of the products with the description in lines 37-39. **Proposed change**: The quality data requirements presented in this guideline are applicable to all applications for biological veterinary medicinal products **(including IVMPs)** ~~(biological other than IVMPs and IVMPs)~~ that are limited market products as defined by Article 4(29), **whether they meet the requirements of Article 23, or not.**	Accepted. Slightly reworded.
Lines 70-71	1	**Comment:** Article 4(29) should be added as reference. **Proposed change**: This guideline should be read in conjunction with Regulation (EU) 2019/6, in particular **Article 4(29),** Article 8, Article 23 and Annex II.	Accepted.

Line number(s) the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome (if applicable)
Lines 72-77		**Comment:** The information in lines 72-77 should be aligned with the rest of the guideline to clarify that the flexibilities with regards to quality data presented in the guideline are relevant for all products that meet the definition of limited market in Article 4(29), including both applications eligible, and not eligible under Article 23. The sentence "*If a product meets the definition of 'limited market' in Article 4(29) of the Regulation and the application is not eligible for authorisation under Article 23, then a comprehensive set of data will be required"* is therefore confusing and not considered relevant to include in this guideline. It should also be specified that this guidance aims to highlight where general flexibility exists for quality data. **Proposed change**: ~~If a product meets the definition of 'limited market' in Article 4(29) of the Regulation and the application is not eligible for authorisation under Article 23, then a comprehensive set of data will be required.~~ The data requirements provided for in Annex II can accommodate some flexibilities because of the characteristics of the products concerned. This guidance aims to highlight where such general flexibility exists **for quality data** and how this flexibility may be applied to marketing authorisation applications for products ~~intended for limited markets~~ **that meets the definition of limited market in Article 4(29)**, where scientifically justified.	Accepted and updated.
Lines 91-99	1	**Comment:** Giving the definition of a limited market product and the medical need to have it on the market, it is difficult to understand why, if the product and presentation(s) remain the same, additional data should be needed if the product has already been assessed and authorised by another MS (and variations have been submitted to provide for update of the product). **Proposed change**: we propose to delete "~~Other specific data requirements for the limited market product based on an authorised product may also be required depending on adaptations of the existing product to ensure its suitability for the limited market species/indication~~"	Not accepted. The text is considered relevant. An example has been added to clarify the point.
Lines 112-126	1	**Comment:** The references in lines 112-126, focusing on safety and efficacy requirements, are not considered relevant for this guideline and should be deleted.	Accepted.

Line number(s) the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome (if applicable)
		Proposed change: Please delete references in lines 112-126.	
Lines 136-146	1	**Comment:** Refer to the comments to lines 72-77 above. The definitions in lines 136-146 are not considered relevant for this guideline and should be deleted. **Proposed change**: Please delete definitions in lines 136-146.	Accepted.
Line 154 and line 158	1	**Comment:** In footnote 1, which applies to both Table 1 and Table 2, the pilot and R&D batches should be required to be *"representative of"* instead of in *"full compliance with"* the production process described in the licensing dossier. We consider the designation *"representative of"* as more appropriate in this context as small-scale batches obviously will not be in full compliance with the future licensing dossier, e.g. batch size. Representative is aligned with the wording even for consistency batches in Annex II (section IIIb.2. F. Batch-to-batch consistency). **Proposed change***:* [1] Pilot batch: small scale industrial batch **representative of** ~~, but in full compliance with~~ the production process described in the licensing dossier. R&D batch: batch produced under laboratory conditions but **representative of** ~~in full compliance with~~ the production process described in the licensing dossier.	Accepted.
Line 154 and line 158	1	**Comment:** Wording in Table 1 should be aligned with Table 2 where appropriate. Please refer to comments to line 160 below where relevant.	
Table 1 & 2, section 2B	1	**Comment:** Use of pilot or R&D batches is an improvement compared to previously requested consecutive batches, especially as this has already been an option for minor use/minor species (MUMS) guidance. Nevertheless, it is not clear when it is mentioned "at least two pilot scale or R&D batches". Please, confirm that a third batch is not needed for initial submission. Please, confirm that the data for a third batch it may also consist of an additional pilot or R&D batch. Indeed, even for regular biological products (not limited-market products) there is no mandatory requirement in the legislation to provide consistency data for full-scale batches, the requirement should be revised accordingly (i.e., remove the need for full-scale). **Proposed change to add clarification**. Tables 1&2:	Partially accepted. The text has been revised as follows: Results of one full-scale batch (for standard manufacturing methods) or two full-scale batches (for non-standard manufacturing methods) should be provided post

Line number(s) the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome (if applicable)
		Use of at least two pilot scale or R&D[1] batches ~~acceptable~~ **for active substance and finished product** ~~to validate the consistency of production process for the finished product~~ acceptable to validate the consistency of production process for the finished product (**to be completed with** the results of one additional ~~the two first full-scale~~ batch post authorisation (as a Post Approval Measure). At least two active substance batches should be present~~ed~~ in the ~~three~~ finished product batches." ~~Results of the two first full-scale batches post authorisation (PAM - recommendation).~~	authorisation.
Table 1and 2, section 2D	1	**Comment:** The requirement in section 2.D should be clarified to show that either an evaluation of existing data or new validation data should be provided for control tests, for parameters considered critical to the manufacturing process. By this requirement we also understand that for control tests for parameters considered non-critical to the manufacturing process, evaluation or validation data may not be required (if justified). **Proposed change:** Evaluation **or** ~~/~~validation data for control tests for parameters considered critical to the manufacturing process**.**	Partially accepted. The text has been amended to increase clarity: New validation data or the evaluation of existing validation data for control tests for parameters considered critical to the manufacturing process.
Table 1, section 2E	1	**Comment:** the approach to use surrogate testing is welcome. This concept is however not clearly defined in the veterinary guidelines and may benefit from some further clarification. **Proposed change:** A clearer statement would be appreciated.	Accepted. The text has been amended to increase clarity: Surrogate testing can be used to determine potency of each batch if adequately linked to the biological/functional effect of the active substance. The surrogate test can be

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			run routinely for release to avoid having to run the activity test.
Table 1 & 2, section 2F	1	**Comment:** Use of pilot or R&D batches is an improvement compared to previously requested consecutive batches, especially as this has already been an option for minor use/minor species (MUMS) guidance. Nevertheless, it is not clear when it is mentioned "at least two pilot scale or R&D batches". Please, confirm that a third batch is not needed for initial submission. Please, confirm that the data for a third batch it may also consist of an additional pilot or R&D batch. **Proposed change to add clarification**. Tables 1&2: Active substance (comments column): Use of at least two pilot scale or R&D[1] batches. ~~Two active substance batches required.~~ Finished product (comments column): Use of a*t least two pilot scale or R&D[1] batches* (**to be completed with** the results of one additional ~~the two first full-scale~~ batch, post authorisation (as a Post Approval Measure). ~~Results of two full-scale batches post authorisation (PAM - recommendation)~~	Partially accepted. Text amended as follows: Finished product: Use of at least two pilot scale or R&D[1] batches. Results of one full-scale batch (for standard manufacturing methods) or two full-scale batches (for non-standard manufacturing methods) should be provided post authorisation.
Table 1 & 2, section 2G	1	**Comment:** Please see previous comments on the use of pilot or R&D batches. It is suggested to change the requirement regarding finished product container to be in line with the former requirement in EMA/CVMP/IWP/123243/2006-Rev.3 *(Guideline on data requirements for immunological veterinary medicinal products intended for minor use or minor species (MUMS)/limited market)*. Shelf life of the injectable product after broaching: in the current regulation it is mentioned that "*In the case of multi-dose containers, where relevant, stability data shall be presented to justify a shelf life for the product after it has been broached or opened for the first time and an in-use specification shall be defined*". We are of the opinion that this wording allows to introduce the reduction from the previous MUMS guideline, and it could be applicable too for	Partially accepted. The text has been revised as follows: Finished product: Use of at least two pilot scale or R&D[1] batches. Stability data for each final container material type should be provided but stability data on one final container size is

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		biological veterinary medicinal products other than immunological: "when in-use-shelf life is necessary, if it can be provisionally based on experience with other vaccines, the data can be subject to a post authorisation commitment". We also suggest harmonising the comments for table 2 with the ones of table 1. **Proposed change to add clarification**. *Active substance (comment column):* Use of at least two pilot scale or R&D[1] batches ~~acceptable~~. Two active substance batches required. *Finished product (comment column):* Use of at least two pilot scale or R&D[1] batches ~~acceptable . Two active substance batches required.~~ (**to be completed with** the results of one additional ~~the two first full scale~~ batch, post authorisation (as a Post Approval Measure). **Stability data for each final container material type should be provided but stability data on one final container size is acceptable provided the selected presentation is justified by the applicant**. ~~Minimum and maximum container acceptable (containers are made of the same materials incl. stoppers).~~ ~~Stability results of two full-scale batches provided post-authorisation (PAM – recommendation).~~ **When in-use-shelf life is necessary, if it can be provisionally based on experience with other biological veterinary medicinal products other than immunological, the data can be subject to a post authorisation commitment**	acceptable provided the selected presentation is justified by the applicant. Stability results of one full-scale batch (for standard manufacturing methods) or two full-scale batches (for non-standard manufacturing methods) should be provided post authorisation. Stability data for minimum and maximum container (containers are made of the same materials incl. stoppers) to be provided post authorisation.