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# Guideline on quality data requirements for applications for veterinary medicinal products other than biologicals intended for limited markets

Draft

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**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
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# Guideline on quality data requirements for applications for veterinary medicinal products other than biologicals intended for limited markets

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# Executive summary

The general aim of this guidance is to define acceptable data requirements for the demonstration of quality of veterinary medicinal products other than biologicals classified as limited markets in line with Article 4(29) of Regulation (EU) 2019/6.

It is the intention of the guidance to indicate which data flexibilities within Annex II to Regulation (EU) 2019/6 can be availed of for 'limited market' products.

# 1. Introduction (background)

The importance of the availability of veterinary medicinal products is well recognised in the EU. Veterinary medicinal products legislation has been revised with the aim of reducing the administrative burden, enhancing the internal market and increase the availability of veterinary medicinal products, while guaranteeing the highest level of public and animal health and environmental protection.

This led to the introduction of specific provisions for limited markets in Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products repealing Directive 2001/82/EC (the Regulation). Article 4(29) of the Regulation provides a definition for limited market and Article 23 allows for the possibility to waive the submission of safety and efficacy data when certain conditions are met.

For the reasons indicated above related to availability of veterinary medicines, it is beneficial from scientific and practical perspectives to provide guidance describing how the general quality data requirements in Annex II can also be adapted to products that meet the definition of limited market in Article 4(29) due to the characteristics of these products.

The guidance provided in this document is general. However, if during product development, an applicant wishes to have clarity on specific data requirements for an application relating to a specific veterinary medicinal product, Scientific Advice is available upon request.

# 2. Scope

The purpose of this scientific guidance is to indicate how the general flexibilities provided within 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. That is, while there is an obligation that the dossier complies with the requirements of Annex II, when scientifically justified, the general flexibility vis-à-vis data requirements can be applied for such products within the existing bounds of Annex II.

The quality data requirements presented in this guideline are applicable to all applications for limited market products as defined by Article 4(29), regardless of their legal basis, except for informed consent applications under Article 21 as the technical documentation on quality, safety and efficacy of those applications is the same as that of an already authorised veterinary medicinal product.

# 3. Legal basis

This guideline should be read in conjunction with Regulation (EU) 2019/6, in particular Article 8, Article 23 and Annex II.

# 4. Specific requirements for applications for limited market products

## *4.1. Application based on an existing veterinary medicinal product*

A marketing authorisation application based on an existing veterinary medicinal product may be an application for a different target species, a different strength, a different dosage form, a new route of administration, a new indication or a combination of more than one of these changes, compared to those already approved in the existing veterinary medicinal product, resulting in a new marketing authorisation for the limited market product. 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. Other specific data requirements for the limited market product based on an authorised product may also be required and will be dependent on the adaptations required to the existing product to ensure its suitability for the limited market species/indication.

### 4.1.1. No change to strength, dosage form or route of administration

The following data should be provided for a marketing authorisation application for the limited market product:

1. The marketing authorisation number of the authorised veterinary medicine.
2. The member state in which the veterinary medicine is authorised and the date this authorisation was issued.
3. The current agreed SPC for the authorised veterinary medicine.
4. A full copy of the quality part of the dossier for the authorised veterinary medicine.
5. An additional TSE risk assessment if the limited market product is to be used in a species susceptible to TSEs.
6. A review of the control strategy (e.g. for mutagenic and/or elemental impurities) as relevant to demonstrate suitability of the existing controls in place taking into account the new posology and target species.
7. Where relevant, data to establish that accurate dosing of the product can be achieved and to demonstrate that the integrity of the product will not be compromised by a modified pattern of use. Appropriate SPC statements designed to ensure accuracy of dosing should be proposed and justified.
8. The relevance of the existing in-use studies should be discussed and if necessary, new ones provided.
9. A declaration that other than the data listed above, or additional new data specifically identified in the application, Part 2 of the dossier is the same as that of the authorised veterinary medicinal product.

Items 1 to 3 above are provided to demonstrate that the proposed product is identical to the EU authorised veterinary medicinal product. Item 4 will not be assessed. Items 5-9 will be reviewed and assessed.

Items 1 to 3 and item 9 should be located in the VNeeS 'add-info' folder and the remaining items should be located in the relevant section of Part 2.

Examples of where the existing in-use studies may not be directly relevant and where additional supporting data may be required include:

- For a veterinary medicine intended for incorporation into feed, inclusion rates and the nature of the feed into which the veterinary medicinal product will be incorporated may differ depending on the species. Additional homogeneity and stability studies may be required.
- For a water-soluble powder intended for administration in the drinking water inclusion rates may differ to take account of differences in water uptake and the desired dose in different species. Depending on the extent of any differences, further solubility and in-use stability studies may be required.

For multidose products, it is likely that in most instances, it will be possible to measure and administer the required dose in accordance with the posology for the specific limited market species/indication, for example using appropriately graduated syringes. Appropriate recommendations for the SPC and the product literature should be proposed by the Applicant. 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. Where dose volumes will be significantly lower in the limited market product, it may be desirable to add a smaller volume container to the range of pack sizes. However, the existing pack sizes could be used, with the addition of appropriate warnings on the SPC and product literature.

For unit dose products, such as unscored tablets, if the bodyweight of the authorised target species is significantly higher than that of the proposed target species, in order to avoid overdosing, it may be necessary to develop and register with appropriate supporting quality data a more suitable strength of the existing product. However, where the bodyweight of the authorised target species is significantly lower than that of the proposed target species, it will usually be possible to deliver the desired dose to the proposed target species simply by using multiple numbers of the unit dose product.

### 4.1.2. Change in strength, dosage form or route of administration

To authorise a product for limited market species based on an existing quality dossier for an already authorised veterinary medicinal product but with a different strength, dosage form or route of administration, solely for use in a limited market, cross-reference to the existing Part 2 will be allowed where applicable. When the excipients are the same, their proportions are similar and the proposed packaging material is the same, some possible flexibilities in the usual supporting quality data requirements may be acceptable as follows:

*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.
- For non-standard processes, validation data on 1 full scale batch would be acceptable if supported by validation data on 2 pilot scale batches.

*Final product batch analysis data*

- Data for 2 batches of at least pilot scale.

In case more than one site is proposed, batch data are required for each site. The number of required batches depends on the kind of process and differences between the sites.

*Final product stability*

- Data for 2 batches of at least pilot scale.
- Post approval stability data on production batches not required (apart from those defined by the EU GMP requirements on ongoing stability studies) as long as stability data are available on pilot batches (to grant a shelf life).
- If an existing strength of the product showed no significant change when stored at 40 ºC/75% RH, samples may be stored at 25 ºC/60% RH only and the storage instructions on the SPC should be the same as those already authorised for the existing strength of the product. Where the existing strength of the product did show significant change under accelerated storage conditions, then the new strength of the product must be stored under real time and accelerated conditions in accordance with the relevant CVMP guidelines.
- The use of bracketing/matrixing is recommended, where applicable.
- Photostability data not required as long as the product is provided in a carton (or other suitable protective packaging) and the product information includes a storage precaution to protect from light.

### 4.1.3. Variations requiring assessment

Changes according to section 4.1.1 and 4.1.2 can also be submitted as a variation requiring assessment and in those cases submission of all the data indicated in the aforementioned sections is not necessary. Information detailed in section 4.1.1 (items 1-4) is not needed. Only additional quality data to support the limited market application should be submitted and flexibilities indicated in section 4.1.2 can be applied.

## *4.2. Application based on existing human medicinal product for use in a limited market*

If a human medicine is already authorised in the EU and has been assessed for conformance with the quality requirements for human medicine, an acceptable quality dossier already exists for the product and the assessment of the core quality data will not be repeated by the veterinary competent authority(ies).

The supporting quality data which would be routinely assessed would be those dealing with the use of the product in the limited market.

The following data should be provided for the limited market product:

1. The marketing authorisation number of the authorised human medicine.
2. The member state in which the human medicine is authorised and the date this authorisation was issued.
3. The current agreed SmPC for the authorised human medicine.
4. A full copy of the quality part of the dossier as submitted to the relevant human regulatory authority with the initial application, taking account of any responses to questions and subsequent post-approval changes.

5. An additional TSE risk assessment if the limited market product is to be used in a species susceptible to TSEs.

6. A review of the control strategy (e.g for mutagenic and/or elemental impurities) as relevant to demonstrate suitability of the existing controls in place taking into account the new posology and target species.

7. Where relevant, data to establish that accurate dosing of the product can be achieved and to demonstrate that the integrity of the product will not be compromised by a modified pattern of use. Appropriate SPC statements designed to ensure accuracy of dosing should be proposed and justified.

8. Supplementary in-use studies as appropriate (see section 4.1.1 above).

9. If the finished product manufacturing site for the veterinary product is different from that for the human product, batch data from 2 batches of at least pilot scale should be provided. In addition, for standard processes, a process validation scheme and evaluation/validation data for critical parameters on at least 1 pilot scale batch should be provided. For non-standard processes, validation data on 1 full scale batch would be acceptable if supported by validation data on 2 pilot scale batches.

10. A declaration that other than the data listed above, or additional new data specifically identified in the application, the quality part of the dossier is the same as that of the authorised human medicinal product.

Items 1 to 3 above are required to demonstrate that the proposed product is identical to the EU authorised human medicine. Item 4 will not be assessed. Items 5 to 10 will be reviewed and assessed.

Items 1 to 3 and item 10 should be located in the VNeeS 'add-info' folder and the remaining items should be located in the relevant section of Part 2.

Following approval, variations to the authorised limited market product, with supporting data should be submitted in accordance with legislation for veterinary medicinal products. Evidence of approval of a variation by the competent authority for human medicines will be taken into consideration during the assessment of the variation in the context of the veterinary limited market product.

Note:

There may be some situations where a human medicinal product could not be authorised for use in animals. This will particularly be the case when considering unit dose products intended for use in a lower bodyweight target species. Crushing and dilution of tablets/capsules cannot be condoned. Equally dilution of injections cannot be supported. However, steps such as: the use of syringes designed to measure very low volumes of an injection (for example those more usually used to administer insulin); use of scored tablets, can be acceptable.

## *4.3. Application for entirely new veterinary medicine for use in a limited market*

When a marketing authorisation is sought for a new veterinary medicine for use in a limited market, the following are the areas in which some possible flexibilities in the data requirements might be considered:

*Active substance batch analysis data*

- Data required for 2 batches of at least pilot scale.

*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.
- For non-standard processes, validation data on 1 full scale batch would be acceptable if supported by validation data on 2 pilot scale batches.

*Final product batch analysis data*

- Data required for 2 batches of at least pilot scale.

In case more than one site is proposed, batch data are required for each site. The number of required batches depends on the kind of process and differences between the sites.

*Final product stability*

- Data required for 2 batches of at least pilot scale.
- First 2 production scale batches (usually post authorisation) to be subjected to stability testing.
- The use of bracketing/matrixing is recommended, where relevant.
- Photostability data not required as long as the product is provided in a carton (or other suitable protective packaging) and the product information includes a storage precaution to protect from light.

# Definitions

For the purpose of the present guideline, the following definitions apply:

**Limited market**

According to Article 4(29) of Regulation (EU) 2019/6, "'*Limited market' means a market for one of the following medicinal product types:*

*(a) veterinary medicinal products for the treatment or prevention of diseases that occur infrequently or in limited geographical areas;*

*(b) veterinary medicinal products for animal species other than cattle, sheep for meat production, pigs, chickens, dogs and cats".*

**Limited market product eligible for Article 23**

Where the applicant provides evidence that a veterinary medicinal product is intended for a limited market **and** the benefit of the availability on the market of that product to the animal or public health outweighs the risk inherent in the fact that certain documentation has not been provided (satisfies the conditions under Article 23(1)(a) of Regulation (EU) 2019/6).

**Limited market product as defined by Article 4(29), but not eligible for Article 23**

Where the applicant provides evidence that a veterinary medicinal product is intended for a limited market **but** the benefit of the availability on the market of the veterinary medicinal product to the animal or public health does not outweigh the risk inherent in the fact that certain documentation has not been provided (does not satisfy the conditions under Article 23(1)(a) of Regulation (EU) 2019/6).

# References

The following legislation, guidelines and notes for guidance are relevant to this guideline:

- Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02019R0006-20220128
- 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) https://www.ema.europa.eu/en/veterinary-regulatory/research-development/veterinary-limited-markets/guidance-under-veterinary-medicinal-products-regulation/classification-product-intended-limited-market-eligibility-authorisation-under-article-23-regulation#reflection-paper-section
- Concept paper on scientific guidelines for limited market products deemed not eligible for authorisation under Article 23 of Regulation 2019/6 (EMA/CVMP/435071/2021) https://www.ema.europa.eu/en/scientific-guidelines-limited-market-products-deemed-not-eligible-authorisation-under-article-23
- Guidance on the details of the classification of variations requiring assessment according to Article 62 of Regulation (EU) 2019/6 for veterinary medicinal products and on the documentation to be submitted pursuant to those variations https://www.ema.europa.eu/en/veterinary-regulatory/post-authorisation/variations/variations-guidance-under-veterinary-medicinal-products-regulation/variations-requiring-assessment-veterinary-medicines#guidance-section