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Guideline on quality data requirements for applications for biological veterinary medicinal products intended for limited markets

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Executive summary

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) introduced specific provisions for limited markets. Article 4(29) of the Regulation provides a definition for limited market and Article 23 provides specific derogations on the submission of safety and efficacy data when certain conditions applicable to marketing authorisation applications for limited markets are met.

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.

1. Introduction

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 increasing 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 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 the possibility to waive the submission of safety and efficacy data when certain conditions are met.

For the reasons indicated above related to the 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 VMP, 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 biological veterinary medicinal products (biological other than IVMPs and IVMPs) that are limited markets products as defined by Article 4(29).

3. Legal basis

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

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 and how this flexibility may be applied to marketing authorisation applications for products intended for limited markets, where scientifically justified.

Of note, in section IIIa of Annex II of the Regulation, a general statement on flexibility is included: "flexibility is allowed regarding compliance to the requirements specified in this section, but any deviations from the requirements in this Annex shall be scientifically justified and based on specific properties of the biological product".

Applicants should also refer to other relevant European and VICH guidelines listed in the references section.

4. Data requirements

Generally, the requirements as provided in section IIIa.2 and IIIb.2 of Annex II to Regulation 2019/6 and the relevant European Pharmacopoeia (Ph. Eur.) general chapters and monographs apply to all biological veterinary medicinal products, including those for limited markets. The CVMP, joint CVMP/CHMP and VICH guidelines concerning quality are also applicable for limited market products. The practical application thereof to specific dossiers will require a case-by-case assessment.

Applications for limited market products can be based on an existing biological veterinary medicinal product or are an entirely new biological veterinary medicinal product for use in a limited market as defined by Article 4(29). In the case, that an application for a limited market product will be submitted based on an already authorised product, a satisfactory set of supporting quality data already exists for the product. 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 depending on adaptations of the existing product to ensure its suitability for the limited market species/indication.

In Table 1 and 2, possible flexibilities concerning quality data requirements as described in Annex II, section IIIa or section IIIb, are highlighted and commented how this flexibility may be applied to marketing authorisation applications for products intended for limited markets.

5. References

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

1. 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

2. 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

3. Guideline on data requirements for applications for immunological veterinary medicinal products intended for limited markets submitted under Article 23 of Regulation (EU) 2019/6 - (EMA/CVMP/59531/2020)

   https://www.ema.europa.eu/en/data-requirements-applications-immunological-veterinary-medicinal-products-intended-limited-markets

4. Guideline on efficacy and target animal safety data requirements for applications for non-immunological veterinary medicinal products intended for limited markets submitted under Article 23 of Regulation (EU) 2019/6 - (EMA/CVMP/52665/2020)

   https://www.ema.europa.eu/en/efficacy-target-animal-safety-data-requirements-applications-non-immunological-veterinary-medicinal

5. Guideline on safety and residue data requirements for applications for non-immunological veterinary medicinal products intended for limited markets submitted under Article 23 of Regulation (EU) 2019/6 - (EMA/CVMP/345237/2020)

   https://www.ema.europa.eu/en/safety-residue-data-requirements-applications-non-immunological-veterinary-medicinal-products

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 been provided (satisfies the conditions under Article 23(1)(a)(b) 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).

Biological veterinary medicinal product

According to Article 4(6) of Regulation (EU) 2019/6 a *'Biological veterinary medicinal product' means a veterinary medicinal product where an active substance is a biological substance.*

Immunological veterinary medicinal product

According to Article 4(5) of Regulation (EU) 2019/6 an *'Immunological veterinary medicinal product' means a veterinary medicinal product intended to be administered to an animal in order to produce active or passive immunity or to diagnose its state of immunity.*

Table 1: Possible flexibility concerning quality data requirements for biological veterinary medicinal products other than immunological veterinary medicinal products in Annex II

Please note that the numbering of the table refers to the numbering in Section IIIa of Annex II to Regulation 2019/6.

No. of section	Section title	Data requirements	Comment on possible reduction
2.B	Description of the manufacturing method	Validation of the production process as a whole shall be demonstrated with provision of results of three consecutive batches produced using the method described.	Use of at least two pilot scale or R&D[1] batches acceptable to validate the consistency of production process for the finished product. At least two active substance batches should be presented in the three finished product batches. Results of the two first full-scale batches post authorisation (PAM - recommendation).
2.D	Control tests during the manufacturing process	Validation of the control tests shall be provided, unless otherwise justified.	Evaluation/validation data for control tests for parameters considered critical to the manufacturing process.
		A test for biological activity shall be included, unless otherwise justified.	
2.E	Control tests on the finished product	An activity test or test for quantification of the active substance or test to quantitatively measure the functionality (biological activity/functional effect) which is linked to relevant biological properties shall be implemented to show that each batch will contain the appropriate potency to ensure its safety and efficacy. A biological assay shall be obligatory when physicochemical methods do not provide adequate information on the quality of the product.	Surrogate testing can be used and may not be used for each batch.

[1] Pilot batch: small scale industrial batch, but in **full compliance with the production process described in the licensing dossier**.
R&D batch: batch produced under laboratory conditions but in **full compliance with the production process described in the licensing dossier**

No. of section	Section title	Data requirements	Comment on possible reduction
2.F	Batch-to-batch consistency	Active substance In order to ensure that quality of the active substance is consistent from batch to batch and to demonstrate conformity with specifications data from representative batches shall be provided.	Use of at least two pilot scale or R&D[1] batches acceptable. Two active substance batches required.
		Finished product In order to ensure that quality of the product is consistent from batch to batch and to demonstrate conformity with specifications a full protocol of three consecutive batches representative of the routine production shall be provided.	Use of at least two pilot scale or R&D[1] batches acceptable. Results of two full-scale batches post authorisation (PAM - recommendation)
2.G	Stability tests	Stability data of the active substance may be obtained either through testing of the active substances themselves or through appropriate testing of the finished product.	Use of at least two pilot scale or R&D[1] batches acceptable. Two active substance batches required.
		Tests shall be carried out on not fewer than three representative batches produced according to the described production process and on products stored in the final container(s).	Use of at least two pilot scale or R&D[1] batches acceptable. 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).
		Stability data obtained from combined products may be used where adequately justified for derivative products containing one or more of the same components.	
		Information on the efficacy of preservatives in other similar biological veterinary medicinal products from the same manufacturer may be sufficient.	

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Table 2: Possible flexibility concerning quality data requirements for immunological veterinary medicinal products in Annex II

Please note that the numbering of the table refers to the numbering in Section IIIb of Annex II to Regulation 2019/6.

No. of section	Section title	Data requirements	Comment
2.B	Description of the manufacturing method	Validation of all the methods of control used in the manufacturing process shall be described, documented and the results provided, unless otherwise justified.	
		Validation of the production process as a whole shall be demonstrated with provision of results of three consecutive batches produced using the method described.	Use of at least two pilot scale or R&D[1] batches acceptable to validate the consistency of production process for the finished product. At least two active substance batches should be presented in the finished product batches. However, at least two batches should be of different composition regarding the harvest material. Results of the two first full-scale batches post authorisation (PAM – recommendation).
2.D	Control tests during the manufacturing process	Validation of the control tests shall be provided, unless otherwise justified.	Evaluation/validation data for control tests for parameters considered critical to the manufacturing process.

No. of section	Section title	Data requirements	Comment
2.F	Batch-to-batch consistency	A full protocol of three consecutive batches representative of the routine production giving the results for all tests performed during production and on the finished product shall be provided.	Use of at least pilot scale or R&D[1] batches acceptable. At least two active substance batches should be presented in the finished product batches. Results of the two first full-scale batches post authorisation (PAM – recommendation).
		Consistency data obtained from combined products may be used for derivative products containing one or more of the same components.	
2.G	Stability tests	Stability tests for the finished product shall be carried out on not fewer than three representative batches produced according to the described production process and on products stored in the final container(s).	Use of at least two pilot scale or R&D[1] batches acceptable. Minimum and maximum container acceptable (containers are made of the same materials incl. stoppers). Stability results of three full-scale batches post-authorisation (PAM – recommendation).
		Stability data obtained from combined products may be used where adequately justified for derivative products containing one or more of the same components.	
		Information on the efficacy of preservatives in other similar immunological veterinary medicinal products from the same manufacturer may be sufficient.	
		Stability data of the active substances may be obtained either through testing of the active substances themselves or through appropriate testing of the finished product.	Use of at least two pilot scale or R&D[1] batches acceptable. Two active substance batches required.

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