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Committee for Veterinary Medicinal Products (CVMP)

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

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This guideline replaces the Guideline on efficacy and target animal safety data requirements for veterinary medicinal products intended for minor use or minor species (MUMS)/limited market (EMA/CVMP/EWP/117899/2004–Rev.1).

Keywords	**Availability, limited market, classification, Article 23, Article 24, eligibility, Regulation (EU) 2019/6, non-immunological veterinary medicinal products, efficacy, target animal safety, data requirements**

[1] Rev.1 introduces changes to Section 7 'Summary of Product Characteristics', i.e. an additional sentence to be carried by the SPCs of veterinary medicinal products authorised under Article 23 of Regulation (EU) 2019/6 has been included.

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Table of contents

Executive summary

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 introduces specific provisions for applications for limited markets (Article 23).

The general aim of this guideline is to define acceptable data requirements for efficacy and target animal safety in case of marketing authorisation applications for non-immunological veterinary medicinal products intended for limited markets submitted under Article 23 of Regulation (EU) 2019/6.

It is the intention of the guideline to indicate which data requirements can be reduced for this type of application; however, it is recognised that this is not always feasible as not all scenarios can be addressed in a general guidance document.

The data requirements for efficacy and target animal safety are presented in Sections 5 and 6 of the guideline.

1. Introduction

From 2006 to 2017, the CVMP developed guidelines on data requirements for MUMS/limited market veterinary medicinal products (VMPs) for quality, safety and efficacy for pharmaceuticals with the aim to stimulate research, development and innovation of new veterinary medicines intended for minor uses and minor species (MUMS/limited markets). Those guidelines were developed with the purpose of reducing 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 benefit-risk balance for the product.

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 introduces specific provisions for limited markets. The current limited markets guidelines have been drafted in line with the new legal provisions, including consideration of data requirements for biological VMPs other than immunological VMPs.

The general aim of this guideline is to define acceptable data requirements for efficacy and target animal safety for VMPs intended for limited markets submitted under Article 23 of Regulation (EU) 2019/6.

It is the intention of the guideline to indicate which data requirements can be reduced for applications submitted in accordance with Article 23 of Regulation (EU) 2019/6, to facilitate the applicant's work for estimating the required resources needed for a limited market application and preparing the application dossier, and provide for predictability. However, it is recognised that this is not always feasible as not all scenarios can be addressed in a general guidance document.

The requirements will depend on the product (active substance, mode of action) and the availability of information (published literature, data in other species, other indications). The guidance provided in this document is general. However, if, during product development, an applicant wishes to have clarity on precise data requirements for an application relating to a specific VMP, Scientific Advice is available upon request.

All pre-clinical *in vivo* studies conducted by an applicant to support an application for marketing authorisation should be in accordance with the requirements of Directive 2010/63/EU on the protection of animals used for scientific purposes and the 3Rs principles of replacement, reduction and refinement (EMA/CHMP/CVMP/JEG-3Rs/450091/2012; EMA/CHMP/CVMP/3Rs/164002/2016).

2. Scope

This guideline applies to marketing authorisation applications for VMPs other than immunological VMPs (i.e. VMPs other than biological VMPs and biological VMPs other than immunological VMPs) intended for limited markets submitted under Article 23 of Regulation (EU) 2019/6.

According to the Annex II to Regulation (EU) 2019/6, a novel therapy VMP could also fall into the category of VMPs other than biological VMPs or in the category of biological VMPs other than immunological VMPs. Thus, the current guideline also applies to these cases.

The objective of this guideline is to clarify the requirements for applications for limited markets deemed eligible for consideration for authorisation under Article 23 of Regulation (EU) 2019/6.

For guidance on the approach to determining eligibility for authorisation under Article 23, and the type of products that may be considered eligible (or ineligible), the reader is referred to the CVMP 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) (EMA/CVMP/235292/2020).

3. Definitions

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.*

Clinical trial

According to Article 4(17) of Regulation (EU) 2019/6, a '*Clinical trial' is a study which aims to examine under field conditions the safety or efficacy of a veterinary medicinal product under normal conditions of animal husbandry or as part of normal veterinary practice for the purpose of obtaining a marketing authorisation or a change thereof.*

Pre-clinical study

According to Article 4(18) of Regulation (EU) 2019/6, a 'pre-clinical study' is a study not covered by the definition of clinical trial which aims to investigate the safety or efficacy of a veterinary medicinal product for the purpose of obtaining a marketing authorisation or a change thereof.

Exploratory trials / pilot studies

Precursors to confirmatory trials. A pilot study is a small-scale preliminary study conducted prior to performance of a full-scale research study with a view to determining if something can be done and/or what is the best way to design a study to investigate a particular hypothesis. The specific objectives of a pilot study may be to evaluate feasibility of the study protocol, refine aspects of the study design, determine the acceptability of the intervention, select the most appropriate primary outcome measure and/or obtain preliminary data for sample size calculation.

Biological veterinary medicinal products

According to Article 4(6) of Regulation (EU) 2019/6, a '*Biological veterinary product' means a veterinary medicinal product where an active substance is a biological substance*. A '*Biological substance' is defined as a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with knowledge of the production process and its control* (Article 4(7) of Regulation (EU) 2019/6).

Biological veterinary medicinal products other than immunological veterinary medicinal products

This group contains all biological veterinary medicinal products with the exception of immunological veterinary medicinal products. According to Article 4(5) of Regulation (EU) 2019/6, an '*Immunological veterinary medicinal product' is 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.*

Veterinary medicinal products other than biological veterinary medicinal products

This group contains all veterinary medicinal products where the active substance is not a biological substance; these products were formerly known as "pharmaceuticals".

4. Legal basis

Requirements for a marketing authorisation application are laid down in Article 8(1)(b) of Regulation (EU) 2019/6, and are specified in Annex II to Regulation (EU) 2019/6, Section II for veterinary medicinal products other than biological veterinary medicinal products and Section IIIa for biological veterinary medicinal products other than immunological veterinary medicinal products.

One of the intentions of the legislation in place for the authorisation of veterinary medicines, as laid down in the preamble of Regulation (EU) 2019/6, recital no. 30, is to facilitate the authorisation of veterinary medicinal products intended for limited markets:

"(30) *Companies have less interest in developing veterinary medicinal products for markets of a limited size. In order to promote the availability of veterinary medicinal products within the Union for those markets, in some cases it should be possible to grant marketing authorisations without a complete application dossier having been submitted, on the basis of a benefit-risk assessment of the situation and, where necessary, subject to specific obligations. In particular, the grant of such marketing authorisations should be possible in the case of veterinary medicinal products for use in minor species or for the treatment or prevention of diseases that occur infrequently or in limited geographical areas.*"

In addition, Article 23 of Regulation (EU) 2019/6 introduces a specific legal basis for veterinary medicinal products intended for limited markets, also specifying the conditions which need to be fulfilled by applications for limited markets:

"*1. By way of derogation from point (b) of Article 8(1), the applicant shall not be required to provide the comprehensive safety or efficacy documentation required in accordance with Annex II, if all of the following conditions are met:*

(a) the benefit of the availability on the market of the veterinary medicinal product to the animal or public health outweighs the risk inherent in the fact that certain documentation has not been provided;

(b) the applicant provides the evidence that the veterinary medicinal product is intended for a limited market.

2. Where a veterinary medicinal product has been granted a marketing authorisation in accordance with this Article, the summary of product characteristics shall clearly state that only a limited assessment of safety or efficacy has been conducted due to the lack of comprehensive safety or efficacy data."

This is also reflected in Annex II to Regulation (EU) 2019/6 under Section IV.6 – *Applications for limited markets*:

"*A marketing authorisation may be granted for a limited market in the absence of comprehensive safety and/or efficacy data when, as provided for in Article 23, the applicant demonstrates that the product is intended for use in a limited market and that the benefit of availability of the new product outweighs the risk associated with the omission of some of the safety or efficacy data required by this Annex.*

For such applications, the applicant shall submit Parts 1 and 2 as described in this Annex.

For Parts 3 and 4, some of the safety or efficacy data required by this Annex may be omitted. As regards the extent of safety and efficacy data that may be omitted, the relevant guidance published by the Agency shall be taken into account."

5. Pre-clinical requirements

Pre-clinical studies aim to investigate the pharmacological activity, pharmacokinetic properties, dose and dosing interval, resistance (if applicable) and the target animal tolerance of the product (see also section '3. Definitions – Pre-clinical study' of this guideline).

Interspecies extrapolation of pre-clinical data to support applications for limited markets will be accepted whenever scientifically justifiable (where the pharmacology of the product is comparable between species).

Published literature concerning use of the active substance/product in the proposed or another target species, as well as from other use of the active substance, may be used for the pre-clinical documentation where scientifically justified. However, bibliographic data should be published by a reputable source, preferably peer-reviewed. Appropriate bibliography may include review articles. Inclusion of bibliographic data will, however, need a thorough evaluation as to the reliability and relevance of this information.

5.1. Pharmacology

The mode of action and the pharmacological effects on which the recommended application in practice is based shall be adequately described, including secondary effects (if any).

Basic pharmacokinetic data (to characterise the absorption, distribution and elimination) of the active substance should be provided as a complement to the pharmacodynamic studies to support the establishment of the proposed dosage regimen (route and site of administration, dose, dosing interval, number of administrations, etc.).

Nevertheless, if data (dose confirmation study/clinical trial) is provided to characterise the efficacy and tolerance of the test product in terms of the proposed indication, posology and route(s) of administration, product-specific pharmacokinetic and pharmacodynamic data can be omitted.

5.2. Development of resistance or tolerance to the active substance

Where relevant, information on the potential emergence of resistance or the development of tolerance to the active substance leading to a reduction in effectiveness for the claimed indication in the target animal species should be provided.

5.3. Dose justification/confirmation

Appropriate data should be provided to justify the proposed dose, dosing interval, duration of treatment and any re-treatment interval. In principle, specific dose justification and/or confirmation studies in an appropriate and relevant disease model or in naturally diseased animals should be provided to support the dose regimen of the VMP. For diseases/conditions for which an appropriate disease model does not exist, data relating to exploratory trials/pilot studies in the target animals (either proprietary data or from the published literature) should be provided. Specific dose justification and/or confirmation studies may be omitted where suitable information/data is provided to support the choice of dose.

5.4. Target animal safety

Appropriate data to characterise the safety of the target species to the test product following administration by the proposed route(s) should be provided. Typically, target animal safety (local and systemic) should be confirmed in healthy animals of the target species in a negative-controlled target animal safety (TAS) study implemented under well-controlled laboratory conditions in line with the principles of VICH GL43 in order to characterise signs of intolerance and to establish an adequate margin of safety using the recommended route(s) of administration.

However, the absence of a VICH compliant TAS study may be accepted, if justified, where a comprehensive evaluation of target animal safety is possible by other means, foremostly based on data provided from exploratory and/or clinical trials following administration of the product at the recommended treatment dose and duration of therapy to an adequate number of animals representing the target (sub)species.

Safety data on use in the target species may also be supplemented with reference to use in another relevant species in which the safety profile is expected to be similar, data from toxicity studies in laboratory animals, literature reports and pharmacovigilance data.

6. Clinical trials

For products eligible for authorisation under Article 23 and where it is reasonable to conclude, based on the information provided in accordance with section 5 above, that:

- the product is safe for the target population when administered at the recommended treatment dose and by the proposed route(s) of administration, and
- the product is expected to be effective for the proposed indication in the target diseased animals (that is, there is a reasonable expectation of effectiveness),

the provision of comprehensive clinical documentation including confirmatory clinical trial data will not be required.

Exploratory trials/pilot studies, pre-clinical studies (e.g. dose determination or dose confirmation studies), data stemming from clinical trials conducted outside the European Union along with relevant

information from the published literature may be used to provide information to support the safety and expected efficacy of the product in the absence of comprehensive clinical documentation. However, in the absence of confirmatory clinical trials, the data provided should be adequate to allow a reasonable conclusion to be made on target animal safety and expected efficacy of the VMP.

Where confirmatory clinical trials are provided, these shall be conducted in compliance with established principles of good clinical practice (GCP), unless otherwise justified.

7. Summary of Product Characteristics

Where a veterinary medicinal product has been granted a marketing authorisation in accordance with Article 23 of Regulation (EU) 2019/6, the summary of product characteristics shall clearly state that only a limited assessment of safety or efficacy has been conducted due to the lack of comprehensive safety or efficacy data. In line with Regulation (EU) 2019/6, the SPC will carry the following statement: "*Marketing authorisation granted for a limited market and therefore assessment based on customised requirements for documentation. Only a limited assessment of safety or efficacy has been conducted due to the lack of comprehensive safety or efficacy data.*".

In general, the QRD veterinary annotated product information template is also applicable for veterinary medicinal products granted a marketing authorisation in accordance with Article 23 of Regulation (EU) 2019/6. Standard statements given in the template should be used whenever they are applicable. This concerns the SPC, the labelling and the package leaflet.

Details on the data which have not been provided by the applicant (i.e. the data gaps) will be included and made publicly available in the European public assessment report.

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. CVMP 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) (EMA/CVMP/235292/2020)
3. Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:276:0033:0079:en:PDF
4. Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches (EMA/CHMP/CVMP/JEG-3Rs/450091/2012)
5. Reflection paper providing an overview of the current regulatory testing requirements for veterinary medicinal products and opportunities for implementation of the 3Rs (EMA/CHMP/CVMP/3Rs/164002/2016)
6. CVMP and VICH target animal safety and efficacy guidelines
7. Corrigendum to Commission Notice - Guidance to Applicants - Veterinary Medicinal Products (Official Journal of the European Union C, C/2024/1443, 14 February 2024) (europa.eu)