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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 the Regulation (EU) 2019/6

Draft

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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 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 2019/6.

It is the intention of the guideline to indicate which data requirements can be reduced for this type of applications; 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 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 data provided should be adequate to draw a conclusion of the benefit-risk balance of the product. The guidance provided in this document is general. Applicants are reminded that the Scientific Advice procedure is available to confirm precise requirements for a specific application.

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 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 EMA Reflection paper on classification of a product as intended for a limited market and eligibility for authorisation according to Article 23 (Applications for limited markets).

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.

- *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 of Regulation (EU) 2019/6, Title I for veterinary medicinal products other than biological veterinary medicinal products and Title IIa 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 of Regulation (EU) 2019/6 under Title III (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 of this Regulation, the applicant can demonstrate 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. Preclinical 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.

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 preclinical 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 on 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/clinical study) is provided to characterise the efficacy and tolerance of the test product in terms of the proposed indication, posology and route(s) of administration, specific pharmacokinetic and pharmacodynamic data with the product 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 or pilot studies in the target animals (either proprietary data or from the published literature) should be provided.

5.4. Target animal safety

Appropriate data to characterise the tolerance of the target species to the test product following administration by the proposed route(s) should be provided. Typically, target animal tolerance (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 studies 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.

Tolerance may also be supplemented with reference to use in another relevant species in which tolerance 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/pilot studies, pre-clinical studies (e.g. dose determination or dose confirmation studies), data stemming from clinical trials conducted outside the 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.

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 Article 35(1)(j)(i) of 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*".

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/eli/reg/2019/6/oj
2. CVMP and VICH target animal safety and efficacy guidelines

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000193.jsp&mid=WC0b01ac058002dd32