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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 but not eligible for authorisation under Article 23 of 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 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 limited markets marketing authorisation applications are met.

Products meeting the 'limited market' definition in Article 4(29) of the Regulation but not meeting the conditions listed in Article 23 will require, by default, a comprehensive set of safety and efficacy documentation in accordance with the requirements in Annex II of the Regulation.

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. Specifically, this guideline clarifies the efficacy and target animal safety data requirements for applications for non-immunological veterinary medicinal products intended for limited markets but not eligible for authorisation under Article 23 of Regulation (EU) 2019/6.

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.

Article 23 of the Regulation states that comprehensive safety or efficacy documentation, as defined in Annex II of the Regulation, shall not be required for limited markets applications, provided that the two conditions contained in that same provision are met.

Products meeting the 'limited market' definition in Article 4(29) of the Regulation but not meeting the conditions for limited markets application listed in Article 23 will require, by default, a comprehensive set of safety and efficacy documentation in accordance with the requirements in Annex II of the Regulation.

There is a practical need for specific scientific guidance describing how the general data requirements in Annex II can 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 specific objective of this guideline is to clarify the efficacy and target animal safety data requirements for applications for non-immunological veterinary medicinal products intended for limited markets but not eligible for authorisation under Article 23 of Regulation (EU) 2019/6.

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 on the basis 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.

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

4. General requirements

The requirements for demonstrating efficacy and target animal safety for all applications, including for limited markets, are provided for in Annex II to Regulation (EU) 2019/6. The practical application thereof to specific applications requires a case-by-case assessment. Some factors that will influence the approach selected include the nature of the disease condition, the active substance, the type and availability of animals, availability of information in the published literature, and other practical conditions.

The safety and efficacy of the product under evaluation should be investigated and demonstrated in the target species. Interspecies extrapolation of pre-clinical data will be accepted whenever scientifically justifiable. Where an active substance/product has been authorised for the same or a similar indication in another species, information relating to use in that species can be used in support of the application for a limited market application and, where justified, this may obviate the need for certain studies in the target species, e.g., where the pharmacology (both in terms of pharmacodynamics and pharmacokinetics) of the test product is likely to be comparable between species.

However, there are certain situations where a more comprehensive data package for efficacy and target animal safety might be required, even if a product is classified as limited market, as outlined in the following examples:

- Where a new indication might represent widespread use of the product in a species eligible for limited markets (e.g. a new antiparasitic product for horses);

- Where an active substance is novel in veterinary medicines, and only limited or poor-quality clinical data are available in the target species;
- Where an active substance is novel in the target species, and insufficient information is available to extrapolate from other species;
- Where there are special concerns (e.g. resistance, environmental risk).

Scientific literature, ideally from peer-reviewed journals, reflecting current scientific knowledge may be used to support the efficacy claim. The applicant should ensure that all relevant data, including data publicly available, are not subject to protection of technical documentation.

Should adequate documentation not exist in the literature, the efficacy of the product should be demonstrated in appropriately designed studies. The type and number of studies to be conducted will depend on the deficiencies in available data.

It is recognised that existing pivotal studies may not satisfy current good laboratory/clinical practice (GLP/GCP) requirements. Such studies might nevertheless be considered acceptable if this is justified, and if the design is appropriate to the stated objective of the study.

Where new studies are conducted by the applicant to support the efficacy of a product, they should be conducted to appropriate standards:

- Pharmacological, toxicological, and pre-clinical safety studies should be conducted in conformity with the provisions related to good laboratory practice (GLP);
- Pre-clinical efficacy studies (including dose determination and dose confirmation studies) should follow the requirements for good clinical practice (GCP) and/or good laboratory practice (GLP), as appropriate (depending on the nature of the studies). In case GCP and/or GLP is not applied (e.g. absence of certified GLP status), traceability, accuracy, integrity, and correctness of data should be ensured, and the use of such data in pivotal studies should be justified;
- Clinical trials shall be conducted in accordance with established principles of good clinical practice, unless otherwise justified;
- The applicant should establish appropriate parameters for objectively evaluating efficacy;
- The applicant should test for treatment effects using appropriate statistical methodology. Studies should be designed considering the requirements outlined in the Guideline on statistical principles for clinical trials for veterinary medicinal products (pharmaceuticals) (EMA/CVMP/EWP/81976/2010). It should be possible in all cases to demonstrate a benefit of treatment (either relative to a control or, where appropriate, relative to pre-treatment/baseline data) that is statistically significant. However, the practical limitations of data collection for an infrequently occurring disease will be taken into consideration;
- Ideally, pivotal studies used to support applications for products intended for the treatment of infections or parasitic conditions should be conducted in Europe in order to simulate European conditions of use. Data from studies conducted outside of Europe will be accepted where justified.

5. Specific requirements

5.1. Pre-clinical studies

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 (e.g. 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. Data should be based on scientific literature, e.g. peer-reviewed articles. Inclusion of data derived from literature will, however, need a thorough evaluation as to the reliability and relevance of this information.

5.1.1. Pharmacology

The mode of action and the pharmacological effects on which the recommended application is based shall be adequately described, including secondary effects (if any). In general, 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.) in the target species. See also 'Guideline on conduct of pharmacokinetic studies in target animal species' (EMEA/CVMP/EWP/133/1999).

However, if appropriate data (dose confirmation study/clinical trial) is available to characterise the efficacy and tolerance of the test product in terms of the proposed indication, posology and route(s) of administration in the target species, the need to submit pharmacokinetic / pharmacodynamics studies in the target species could be waived. Instead, the respective product-specific pharmacokinetic and pharmacodynamic properties could be established by other means, e.g. by extrapolation from another species for which the product is authorised, appropriate data from literature, or pilot studies.

In the case of new fixed combinations, if data on the safety and efficacy of an individual known active substance are available to the applicant with sufficient amount of detail, those data could be provided to obviate the need for some studies with the fixed combination, or contributing relevant information. In that case, possible interaction between active substances shall also be investigated.

5.1.2. Development of resistance and related risk in animals

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. A reduction of the dataset is not foreseen.

5.1.3. Dose determination and confirmation

Appropriate data should be provided to justify the proposed dose, dosing interval, duration of treatment and any re-treatment interval.

In principle, dose determination and confirmation studies in an appropriate and relevant disease model and/or in naturally diseased target animals should be provided to support the dosage regimen of the VMP.

For limited market applications, the number of dose determination and/or confirmation studies may be reduced or omitted depending on whether suitable information/data is provided to support the choice of dose and the adequacy of that information/data. In this regard, other data relating to dose determination/confirmation in the target species could be acceptable, such as exploratory trials/pilot studies, data from published literature, or extrapolation from another species for which the product is authorised.

If the efficacy of the product at the recommended dosage regimen has been demonstrated in an adequate and controlled dose confirmation study in the target species, a dose determination study can be omitted.

If a clinical trial has been provided and the selected dose is justified, dose confirmation studies are not required, if the clinical trial includes a control group.

5.1.4. Tolerance in the target animal species

Appropriate data should be provided to characterise local and systemic tolerance of the veterinary medicinal product in the target species following administration by the proposed route.

The requirements for specific target animal safety studies of an application eligible for limited markets will depend on the information available on the safety of the active substance/product in the species eligible for limited markets and/or another species. This information may include data from toxicity studies in laboratory animals, literature reports, pharmacovigilance data, and safety information derived from efficacy studies.

In general, 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.

For substances for which a safety concern exists, a target animal safety study in line with VICH GL43 is considered mandatory.

For products where systemic exposure is known to be negligible, and there are no known safety concerns, a specific target animal safety study is not considered necessary, and tolerance can be demonstrated based on the clinical trial(s) or from published literature data.

Moreover, if the test product is approved for another species and is known to have a wide margin of safety in that species, clinical trial data demonstrating satisfactory tolerance in the target species following administration of the test product at the recommended treatment dose for the recommended duration of therapy may be considered adequate, and a specific target animal safety study may not be required.

Where safety in breeding animals of another species is demonstrated, additional safety data in breeding animals of the target species might not be necessary. However, in the absence of adequate data, a restriction on use in breeding animals (e.g. use in accordance with the benefit/risk assessment of a veterinary surgeon) and offspring may be required.

5.2. Clinical trials

Clinical trials should be conducted using the final formulation and carried out in accordance with established principles of good clinical practice. Experimental data such as exploratory/pilot trials, or results from non-experimental approaches should be confirmed by clinical trials, unless otherwise justified.

Where there is no authorised reference product available or a negatively controlled trial is not feasible, an uncontrolled clinical trial could be acceptable, if justified.

In specific cases, where the efficacy of the test product has been confirmed in dose determination and/or dose confirmation studies and where adequate and robust data are available relating to target animal safety, clinical trials may not be necessary in that species. For example, there might be certain indications/species for a limited market, where a clinical trial would not be required if sufficient pre-clinical data are available. This may be the case for certain rare indications where the conduct of a clinical trial may not be feasible as only a limited number of animals would be available and sufficient efficacy can be ensured from pre-clinical data. In these situations, the absence of clinical trial data must be justified.

In line with Annex II of Regulation (EU) 2019/6, data stemming from clinical trials conducted outside the Union may be taken into consideration for the assessment of an application for a marketing authorisation if the trials were designed, implemented and reported in accordance with the international guidelines on good clinical practice of the VICH and only if the data are sufficiently representative for the Union situation.

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).

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. An exploratory trial / pilot study is a small-scale preliminary study conducted prior to performance of a full-scale research study to allow for data exploration during analysis, contribute to the proof of concept, and to examine the best way to design a study to investigate a particular hypothesis. Additional guidance is provided in the 'Guideline on statistical principles for clinical trials for veterinary medicinal products (pharmaceuticals)' (EMA/CVMP/EWP/81976/2010).

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
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)
3. 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)
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)
5. 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)
6. 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)
7. 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
8. Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches (EMA/CHMP/CVMP/JEG-3Rs/450091/2012)
9. 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)
10. Question and answer document on requirements for pre-clinical studies submitted in support of a marketing authorisation application for a veterinary medicinal product (EMA/CVMP/565615/2021-Rev.1)
11. CVMP and VICH target animal safety and efficacy guidelines