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4 Guideline on efficacy and target animal safety data 5 requirements for veterinary medicinal products intended 6 for minor use or minor species (MUMS)/limited market

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9 This guideline updates the CVMP Guideline on efficacy and target animal safety data requirements for
10 veterinary medicinal products intended for minor uses or minor species/ limited market
11 (EMEA/CVMP/EWP/117899/2004).

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Guideline on efficacy and target animal safety data requirements for veterinary medicinal products intended for minor use or minor species (MUMS)/limited market

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Executive summary

In order to stimulate the development of new veterinary medicines intended for minor uses or minor species (MUMS)/limited market the CVMP developed guidelines on data requirements for MUMS/limited market veterinary medicinal products for quality, safety and efficacy for pharmaceuticals and a guideline for immunologicals. These guidelines are intended to reduce 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.

These MUMS guidelines have now been reviewed and revised with the aim of updating the acceptable data requirements in light of experience gained and clarifying, where appropriate, the applicability of the MUMS data requirements. This guideline describes the data requirements regarding efficacy and target animal safety for pharmaceutical veterinary medicinal products classified as MUMS/limited market.

1. Introduction

For some time there has been considerable concern amongst all parties concerned with animal health in the EU about the lack of authorised veterinary medicinal products for minor uses and for minor species. The availability of safe and effective veterinary medicinal products for minor uses or minor species (MUMS)/limited market will improve both animal welfare, animal health and, in some cases, public health. The Agency at the behest of its Management Board began discussions and consultations on this increasing problem in 1998 and, since that time, the CVMP has worked on the matter and is active in initiatives to address the problem of lack of veterinary medicines.

One of the initial measures introduced by the CVMP was to review data requirements for veterinary medicinal products intended for MUMS, both for pharmaceuticals and immunologicals, and, if possible, to establish standards for demonstration of quality, safety and efficacy for these. A set of CVMP guidelines on data requirements for veterinary medicinal products intended for minor use minor species were finalised in 2006 to 2008 (EMEA/CVMP/QWP/128710/2004, EMEA/CVMP/SWP/66781/2005, EMEA/CVMP/EWP/117899/2004, EMA/CVMP/IWP/123243/2006).

Since then the Agency Policy for classification and incentives for veterinary medicinal products indicated for MUMS/limited markets was established and implemented on 1 September 2009 and updated in December 2014 (EMA/308411/2014). The policy is supported by a guidance document on the classification of veterinary medicinal products indicated for minor use minor species (MUMS) / limited market (EMA/CVMP/388694/2014) providing guidance for implementing the policy and the procedure and criteria for classification of products or applications as MUMS/limited market.

The policy is intended to stimulate the development of new veterinary medicines for minor species and for diseases occurring infrequently or in limited geographical areas in major species that would otherwise not be developed in the current market conditions. The guidelines on data requirements for products classified as MUMS/limited market are an integral part of the policy.

These guidelines are intended to reduce 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.

These guidelines have now been reviewed and revised with the aim of updating the acceptable data requirements in light of experience gained and clarifying, where appropriate, the applicability of the MUMS data requirements.

It is the intention to provide clear guidance under which circumstances data requirements can be reduced for MUMS/limited market products to facilitate the applicant's work for estimating the required resources for a MUMS/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 possible scenarios can be addressed in a general guidance document.

Furthermore, the specific requirements will depend on the data and knowledge available, e.g. there may be scope for reductions if a product has been authorised already for a major species or major use or an MRL has been established for a major species, or if a product concerns an active substance belonging to a well-known class of substances. However, for products containing entirely new active substances, novel therapy products or products representing first in class the possibilities for data reduction are likely to be limited. Similarly, for products presenting a specific risk, e.g. for products containing an antimicrobial or vaccines containing GMOs, the possibility for reducing data requirements will be severely limited in the area related to addressing the risk, i.e. adequate data to justify the indication and establish the appropriate dosage regimen or data to ensure safe and efficacious use of such a vaccine will need to be established, even if the product is classified as MUMS/limited market.

The general aim of this guideline is to define acceptable data requirements for the demonstration of efficacy and target animal safety for veterinary medicinal products intended for minor uses or minor species. In this context, data requirements for the demonstration of efficacy and target animal safety will be influenced to a certain extent by the known pharmacological, toxicological and efficacy profile of an active substance or a related active substance and whether or not the product has been authorised in another species for the same or a similar indication. It follows that 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 may be used in support of the application and, where justified, this may obviate the need for certain studies in the target species. For novel active substances, and for those where limited information is available relating to their use in any animal species, comprehensive information relating to use in the target species will be required.

The guidance provided in this document is general. Applicants are advised to request scientific advice on their individual data package to confirm the precise requirements for their specific application.

2. Scope

This guideline applies to new applications for marketing authorisations of pharmaceutical veterinary medicinal products classified as MUMS/limited market. It also applies for MUMS/limited market applications for line extensions and variations, which can be an extension/variation for a MUMS where the existing product is also for a minor species or a minor use in a major species, but the extension/variation application can be classified as MUMS when the existing product is for a major indication in a major species.

The objective of this guideline is to clarify the requirements for the following applications.

- to provide applicants with information on target animal safety and efficacy data requirements to support applications for authorisation of pharmaceutical veterinary medicinal products intended for minor species;

- to provide applicants with information on target animal safety and efficacy data requirements to support applications for authorisation of pharmaceutical veterinary medicinal products intended for minor uses.

As a general principle, the CVMP and VICH guidelines concerning efficacy are applicable to minor use/minor species products.

3. Definitions

Definitions are provided in the "Revised policy for classification and incentives for veterinary medicinal products indicated for minor use minor species (MUMS)/limited market" (EMA/308411/2014).

Minor species: There is no legislative definition in the EU for major or minor species.

Major species have been defined by the CVMP as follows:

Major food-producing species:

- cattle (dairy and meat animals);
- sheep (meat animals);
- pigs;
- chickens (including laying hens);
- salmon[1].

Major companion animal species:

- cats;
- dogs.

All other animal species, which are not considered major, are as a consequence, by default, classed as minor species.

Minor use: Minor use in a major species is generally considered as the use of veterinary medicinal products for the treatment of diseases that occur infrequently or occur in limited geographical areas and thus are indicated for a smaller market sector.

Limited market: A market for a veterinary medicinal product that is limited in size due to the product being indicated for a disease or condition that represents a minor use in a major species or that occurs in a minor species.

4. Legal basis

Requirements for a marketing authorisation application are laid down in Article 12 of Directive 2001/82/EC, and are specified in Annex I of Directive 2001/82/EC, Title I for pharmaceuticals, as amended by Directive 2009/9/EC.

One of the intentions of the legislation in place for the authorisation of veterinary medicines as laid down in the preambles of Directive 2001/82/EC, preambles No. 9 and 10 of Directive 2004/28/EC, is to facilitate the authorisation of certain veterinary medicinal products:

[1] Salmon should be considered a major species, however other species of the *Salmonidae* family such as rainbow trout should be considered minor species. The term salmon is understood in this context as Atlantic salmon (*Salmo salar*).

"(9) The costs of research and development to meet increased requirements as regards the quality, safety and efficacy of veterinary medicinal products are leading to a gradual reduction in the range of products authorised for the species and indications representing smaller market sectors."

"(10) The provisions of Directive 2001/82/EC also need, therefore, to be adapted to the specific features of the sector, particularly to meet the health and welfare needs of food-producing animals on terms that guarantee a high level of consumer protection, and in a context that provides adequate economic interest for the veterinary medicinal products industry."

This is also reflected in Annex I of Directive 2001/82/EC under Introduction and General Principles.

"(10) In cases of applications for marketing authorisations for veterinary medicinal products indicated for animal species and indications representing smaller market sectors, a more flexible approach may be applicable. In such cases, relevant scientific guidelines and/or scientific advice should be taken into account."

5. General requirements for applications for minor uses or minor species

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. Extrapolation of data from a major to a minor species is most appropriate where the test product is authorised for the same or a similar indication in the major species, and where the pharmacology (both in terms of pharmacodynamics and pharmacokinetics) of the test product is likely to be comparable in both species. 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 may be used in support of the application and, where justified, this may obviate the need for certain studies in the target 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 MUMS:

- Where a new indication might represent a major use of the product in a minor species (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).

Generally, the following information will be required:

- Appropriate data to characterise the mechanism of action and the known pharmacological (including toxicological) effects of the active substance. Consideration should be given to the pharmacokinetic behaviour of the active substance and the effect of route of administration, formulation, etc. on the pharmacological activity of the test product;
- Data to support the recommended treatment dose, duration of therapy and route of administration;
- Appropriate data to characterise the tolerance of the target species to the test product following administration by the proposed route of administration;

- Data to support the efficacy of the product for all proposed indications in the target species.

Literature may be used to support the efficacy claim. Bibliographic data should originate from acknowledged scientific literature ideally from peer-reviewed journals.

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 studies may not satisfy current Good Clinical Practice (GCP) requirements. Such studies may be considered acceptable 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:

- Studies should be conducted in accordance with the principles of GCP;
- Appropriate parameters should be established for objectively evaluating efficacy;
- The applicant should test for treatment effects using appropriate statistical methodology. 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.

6. Specific requirements for products for minor species

6.1. Pre-clinical studies / Dose selection

Interspecies extrapolation of pre-clinical data to support applications for minor species will be accepted whenever scientifically justifiable.

A rationale for the selected treatment regimen and duration of therapy should be provided. The proposed treatment regimen may be justified using:

- Specific dose determination studies, and/or
- Pharmacokinetic and pharmacodynamic (e.g. MIC) data, and/or
- Literature data/results of pilot studies/clinical experience reports, and/or
- Extrapolation from another species for which the product is authorised.

6.2. Target animal safety studies

Appropriate data should be provided to characterise the tolerance of the target species to the test product following administration by the proposed route.

The requirements for specific target animal safety studies in minor species will depend on the information available on the safety of the active substance/product in the minor species 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. For example, if the test product is approved for another species and is known to have a wide margin of safety in that species, field study 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 no/limited data on the safety profile of the active substance in the target species are available, a basic controlled study demonstrating the safety of the (near) final formulation in the target species will be needed. In order to demonstrate a margin of safety in the target species, the study should be designed to investigate tolerance to the product when administered at doses in excess of the recommended treatment dose. The Applicant should justify the study design employed.

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 risk/benefit assessment of a veterinary surgeon) may be required.

6.3. Clinical studies

In principle, a dose confirmation study and a field trial should be provided. Clinical studies should be conducted using the final formulation.

In the absence of specific dose determination studies, the efficacy of the product at the recommended dose regimen should be demonstrated in an adequate and controlled dose confirmation study in the target species. However, if a field study has been provided and the selected dose is justified (see section 5.1), dose confirmation studies might not be required.

Where the efficacy of the test product has been evaluated in the minor species in dose determination and/or dose confirmation studies and where adequate data are available relating to target animal safety, field studies may not be necessary. In such cases, the absence of field studies must be justified.

7. Specific requirements for products for minor uses

The requirements for demonstrating efficacy for minor use indications will be determined on a case-by-case basis. Some factors that will influence the approach selected include the nature of the disease condition, the active substance, the type and availability of the animals, and other practical conditions.

Notwithstanding the case-by-case approach to establishing efficacy requirements for minor use indications, the general requirements as detailed in Section 4 should be satisfied.

For certain minor use products (e.g. products for the treatment of endocrine disorders), the benefit of conducting standard target animal safety studies in healthy animals is questionable because use of the product in healthy animals may not provide a reliable indication of the expected tolerance in the target population associated with normal field use of the product. In such cases, tolerance should be investigated within the scope of field studies on efficacy.

References

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

1. Revised Policy on Classification and Incentives for Veterinary Medicinal Products indicated for Minor use Minor species (MUMS)/limited market

(EMA/308411/2014) http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2014/09/WC500172928.pdf

2. Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products http://ec.europa.eu/health/files/eudralex/vol-5/dir_2001_82/dir_2001_82_en.pdf

3. 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