European Medicines Agency
Veterinary Medicines and Inspections

London, 18 April 2005
EMEA/CVMP/EWP/117899/2004-CONSULTATION

COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE

(CVMP)

GUIDELINE ON

EFFICACY AND TARGET ANIMAL SAFETY DATA REQUIREMENTS FOR VETERINARY MEDICINAL PRODUCTS INTENDED FOR MINOR USES OR MINOR SPECIES

DRAFT AGREED BY EFFICACY WORKING PARTY	20 October 2004
ADOPTION BY CVMP FOR RELEASE FOR CONSULTATION	13 April 2005
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 October 2005

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GUIDELINE ON EFFICACY AND TARGET ANIMAL SAFETY DATA REQUIREMENTS FOR VETERINARY MEDICINAL PRODUCTS INTENDED FOR MINOR USES OR MINOR SPECIES

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1. INTRODUCTION

For some time there has been considerable concern amongst all parties connected with animal health in the EU, especially the veterinary profession, about the decrease in the availability of authorised veterinary medicinal products. This problem is particularly acute in relation to availability of medicines for minor uses/minor species, where there are no authorised products for some uncommonly encountered disease conditions in major species or no authorised products at all for many indications in certain minor species. The EMEA 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 was active in initiatives to address the problem of lack of veterinary medicines.

The CVMP and its Efficacy Working Party (EWP) developed a document called Points to Consider Regarding Availability of Products for Minor Species and Minor Indications (EMEA/CVMP/610/01-Consultation), which was released for public consultation in February 2002. Having reviewed comments received from interested parties following the release of that document, the Committee developed its Position Paper Regarding Availability of Products for Minor Uses and Minor Species (MUMS) (EMEA/CVMP/477/03). That document aims to define the problem in some depth and makes suggestions for possible solutions. The proposals are characterised as short, medium and long-term goals.

One of the main goals for CVMP is to review dossier requirements for veterinary medicinal products intended for minor uses or minor species and, if possible, to establish standards for demonstration of quality, safety and efficacy for these.

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 active substance/product type and whether or not the product has been authorised in a related major 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 a major 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. However, the CVMP is willing to give consideration to the development of specific additional guidance to facilitate the development of specific veterinary medicinal products for minor uses or minor species should proposals for such guidance deemed necessary.

2. SCOPE

The objectives of this document are:

- 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;
- to outline the circumstances under which conditional authorisations for minor uses/minor species products may be approved and to detail the conditions that may be attached to such authorisations.

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2.1 Definitions

Minor species
There is no legislative definition in the EU for major or minor species. However, major species were defined by the CVMP according to animal population data and total consumption figures, using global numbers across Europe for the purpose of CVMP guidelines. Following species are defined by the CVMP as "major": food-producing animals: cattle (dairy and meat animals), sheep (meat animals), pigs, chickens (including laying hens) and *salmonidae;* companion animals: dogs and cats. As a consequence, all other animal species, by default, are classed as minor (see CVMP Position Paper regarding Availability of Products for Minor Uses and Minor Species (MUMS), EMEA/CVMP/477/03-FINAL).

Minor use
There is no legislative definition in the EU for a 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 veterinary medicinal products indicated for a smaller market sector. The minor use of a product will be considered on a case-by-case basis taking into account argumentation put forward by an Applicant to support the minor use of a product (see CVMP Position Paper regarding Availability of Products for Minor Uses and Minor Species (MUMS), EMEA/CVMP/477/03-FINAL).

3. LEGAL BASIS

Requirements for efficacy and target animal safety testing for a marketing authorisation application for a veterinary medicinal product are laid down in Article 12 of European Parliament and Council Directive 2001/82/EC, as amended by Directive 2004/28/EC, and are specified in Annex I of Directive 2001/82/EC, as amended. This Annex is currently under revision.

4. 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.

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;

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

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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 differences 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 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 FOR PRODUCTS FOR MINOR SPECIES

5.1 Pre-clinical studies

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

A rationale for the selected dose, dose range 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 a related major species for which the product is authorised.

5.2 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 a related major species. This information may include literature reports, pharmacovigilance data, and safety information derived from efficacy studies. For example, if the test product is approved for a related major 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.

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In many cases, 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.

In order to establish the safety of veterinary medicinal products intended for use in breeding animals, relevant data are necessary. Otherwise, a label restriction to non-breeding animals will be required.

5.3 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 GCP field study has been provided and pre-clinical data support the selected dose, 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 for certain indications. However, in such cases, it may be a condition of the product authorisation that field data are generated and submitted for evaluation within an agreed time frame post-authorisation (see section 7).

6. 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 nature 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 5 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 in field studies.

7. APPROVAL OF VETERINARY MEDICINAL PRODUCTS IN EXCEPTIONAL CIRCUMSTANCES

Where in respect of particular indications, the Applicant can show that he is unable to provide comprehensive data on therapeutic effect because:

(a) the indications for which the medicinal product is intended are encountered so rarely that the Applicant cannot reasonably be expected to provide comprehensive evidence;
(b) in the present state of scientific knowledge, comprehensive information cannot be provided;

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the marketing authorisation may only be granted subject to the following conditions:

(a) the medicinal product in question is to be supplied on veterinary prescription only and may, in certain cases, be administered only under strict veterinary supervision;
(b) the package insert and any other information must draw the attention of the veterinary practitioner to the fact that in certain specified respects, the particulars available concerning the medicinal product in question are as yet incomplete.

Before approval of a veterinary medicinal product under the circumstances detailed above, the Applicant should provide data/information (from literature or pilot studies) to support an argument for a reasonable expectation of efficacy. Further, reasonable data for establishing a conditional dose must also be provided from the literature or a pilot study. For example, studies conducted in a related species and where a comparable pharmacological profile can be expected may be sufficient to support a conditional dose and a reasonable expectation of efficacy.

Before approval of a veterinary medicinal product under the circumstances detailed above, the Applicant should provide data/information demonstrating that the test product is well tolerated when administered to the target species at, at least, the maximum recommended treatment dose and, where practicable, for the maximum duration of therapy. It is acknowledged that certain products may be indicated for long-term therapy and that, for such products, the provision of safety data for a period equal to the maximum duration of therapy may not be possible.

Approval of a veterinary medicinal product under the circumstances detailed in paragraph 8.1 would only be granted to Applicants who commit to provide supplementary information within an agreed time frame for confirming the efficacy and tolerance of the product.

Upon satisfactory completion of the outstanding data requirements, the product would be granted a full approval. Conversely, where commitments are not fulfilled, or where data generated post-authorisation do not confirm the efficacy and tolerance of the product, the conditional authorisation would be discontinued.

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REFERENCES

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

- Directive 2001/82/EC of the European Parliament and of the Council as amended by Directive 2004/28/EC
- Rules Governing Medicinal Products in the EU: Volume 7A "Guidelines for Efficacy testing of veterinary medicinal products"
- Points to consider regarding availability of products for Minor Species and Minor Indications (EMEA/CVMP/610/01-CONSULTATION)
- CVMP Position Paper regarding availability of Products for Minor Uses and Minor Species (MUMS) (EMEA/CVMP/477/03)
- CVMP efficacy guidelines
- VICH efficacy guidelines

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