European Medicines Agency
Veterinary Medicines and Inspections

London, 20 July 2006
EMEA/CVMP/QWP/128710/2004

COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

GUIDELINE ON

QUALITY DATA REQUIREMENTS FOR VETERINARY MEDICINAL PRODUCTS INTENDED FOR MINOR USES OR MINOR SPECIES

DRAFT AGREED BY QUALITY WORKING PARTY	October 2004
ADOPTION BY CVMP FOR RELEASE FOR CONSULTATION	13 April 2005
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 October 2005
AGREED BY QUALITY WORKING PARTY	February 2006
ADOPTION BY CVMP	20 July 2006
DATE FOR COMING INTO EFFECT	1 February 2007

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 60
E-mail: mail@emea.eu.int http://www.emea.eu.int

GUIDELINE ON QUALITY DATA REQUIREMENTS FOR VETERINARY MEDICINAL PRODUCTS INTENDED FOR MINOR USES OR MINOR SPECIES

TABLE OF CONTENTS

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 the acceptable data requirements for the demonstration of quality for veterinary medicinal products intended for minor uses or minor species.

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 be deemed necessary.

2. SCOPE

The objectives of this guideline are to clarify the requirements for applications for marketing authorisations of pharmaceutical veterinary medicinal products intended for minor species and minor uses.

The four main categories of applications for MUMS are considered to be as follows:

- Existing veterinary medicinal product for use in a minor species.
- Existing veterinary medicinal product for a minor use.
- Existing human medicinal product for use in a minor species or for a minor use.
- Entirely new medicine for use in a minor species or for a minor use.

The application types are listed in order, with the most common scenario appearing at the top of the list. The proposed quality data requirements for each of these categories are set out below.

The scope of this guideline is to cover pharmaceutical veterinary medicinal products but to exclude immunological products.

It should be noted that certain of the proposals contained within this paper may require changes to the current legislation and these have been identified in the text. It is possible that further changes to the legislation may be required to support the various MUMS initiatives being developed by the CVMP and its various working parties. The need for legislative change should not be a barrier would, however, impact on timescales.

As a general principle, the CVMP and joint CVMP/CHMP guidelines concerning quality are applicable to minor species /minor uses products.

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 the European Union for the purpose of CVMP guidelines. All other animal species, which are not considered major, are as a consequence, by default, classed as minor (for details 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 of 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 are indicated for a smaller market sector. The minor use of a product will be considered on a case-by-case basis taking into account justification put forward by an applicant to support the minor use of a product (see Position Paper regarding availability of Products for Minor Uses and Minor Species (MUMS), EMEA/CVMP/477/03-FINAL). Applicants are advised to seek scientific advice from the CVMP before submitting an application.

3. LEGAL BASIS

Requirements for quality for a marketing authorisation application 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.

One of the intentions of the revised legislation for the authorisation of veterinary medicines as laid down in the preambles Nr. 9 and 10 of Directive 2004/28/EC is to facilitate the authorisation of certain veterinary medicinal products:

“(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.”

4. SPECIFIC REQUIREMENTS FOR EACH OF THE DIFFERENT CATEGORIES OF APPLICATIONS FOR MINOR USES AND MINOR SPECIES

4.1 Existing veterinary medicinal product for use in a minor species

Where an EU authorised veterinary medicine already exists, a satisfactory set of supporting quality data already exist for the product. Therefore, there is no requirement for a full part II dossier to be supplied in support of an application to add a minor species to the authorisation where the application is made via a Type II variation or an extension to an existing marketing authorisation. However, in the case of an extension it will be necessary to submit a supplement to the part II dossier that a) confirms that the already authorised part II dossier reflects the currently applied methods for manufacture, control and testing of the product and b) considers the practical use of the medicine in the minor species, to establish if accurate dosing of the product can be achieved and to ascertain if the integrity of the product might be compromised by a modified pattern of use. In particular, the relevance of the existing in-use studies should be reviewed and the number of doses per container must be considered and investigated, if necessary.

Examples of where the existing in-use studies may not be directly relevant and where additional studies may be required include:

- A premix indicated for use in pigs is proposed for use in rabbits. Inclusion rates may differ and certainly the nature of the feedingstuffs into which it will be incorporated will differ. Additional homogeneity and stability studies may be required, unless it can be demonstrated that the existing data are relevant.
- A water soluble powder intended for administration in the drinking water of chickens is proposed for use in a minor species. Inclusion rates may differ to take account of differences in water uptake and the desired dose. Depending on the extent of any differences, further solubility and in-use stability studies may be required.

In the case of a Type II variation, the information described in b) above should be included as part of the supporting data for the variation.

For **multidose products**, it is likely that in most instances, it will be possible to measure and administer the required dose to the minor species, for example using appropriately graduated syringes. Appropriate recommendations for the SPC and the product literature will need to be proposed by the Applicant. In exceptional circumstances, for example for a sterile injection where the required dose volume can not be measured, even with an insulin syringe, it might be necessary to develop and register with appropriate supporting quality data a lower concentration of the existing formulation. An alternative strategy that may be appropriate for non-sterile products is to supply or recommend an appropriate diluent. Data would need to be included in the part II supplement in order to demonstrate that the proposed diluent is suitable. Where dose volumes will be significantly lower in the minor species, it may be desirable to add a smaller volume container to the range of pack sizes. However, as it is likely that the costs involved in this are liable to be prohibitive, therefore the existing pack sizes could be used, but with the addition of appropriate warnings on the SPC and product literature to reduce the risks when using the product to treat minor species.

For **unit dose products**, such as unscored tablets, if the bodyweight of the current target species is significantly higher than that of the proposed minor species (e.g. authorised for dogs, minor species use for guinea pigs), in order to avoid overdosing, it may be necessary to develop and register with appropriate supporting quality data a more suitable strength of the existing product. However, where the bodyweight of the current target species is significantly lower than that of the proposed minor species (e.g. authorised for cats, minor species use for goats), it will usually be possible to deliver the desired dose to the minor species simply by using multiple numbers of the unit dose product.

Where **line extensions** are necessary to introduce a different strength of product solely for use in minor species, a part II dossier will be required. Cross-reference to the existing part II will be allowed where applicable. When the excipients are the same, their proportions are similar and the proposed

packaging material is the same, the usual supporting quality data requirements may be reduced as follows:

Final product process validation data

- For standard and non-standard [1]processes, provision of a process validation scheme only. Thus permitting process validation studies to be conducted on full scale batches post authorisation. The final reports from such process validation studies are to be available for scrutiny during GMP inspections. However, the Licensing Authority must be informed if problems are encountered on validation of the process at the full scale, together with the proposed action.

Final product batch analysis data

- Data for 2 pilot batches only.
- Commitment to be given to inform the Regulatory Authorities immediately if any of the first three production batches fail to meet the agreed Finished Product Specification and to submit these batch analyses data together with the proposed action.

Final product stability

- Data required in application for two pilot batches only.
- No post authorisation stability requirement for production batches (apart from those to be defined by the revision to the EU GMP requirements).
- If the existing strength of the product showed no significant change when stored at 40°C/75%RH, samples may be stored at 25°C/60%RH only and the storage instructions on the SPC should be the same as those already authorised for the existing strength of the product. Where the existing strength of the product did show significant change under accelerated storage conditions, then the new strength of the product must be stored under real time and accelerated conditions in accordance with the relevant CVMP guidelines.
- Concept of bracketing/matrixing to be applied.

4.2 Existing veterinary medicinal product for a minor use

In the majority of such cases the dosage rate and route of administration for the proposed minor use indication will be unchanged and therefore no additional Quality data would be required, except in the case of an extension where a supplement to the part II dossier confirming that the already authorised part II dossier reflects the currently applied methods for manufacture, control and testing of the product.

If the dosage rate and/or route of administration proposed for the minor use are different to those already authorised, then similar sets of circumstances apply, as set out in the above section.

4.3 Existing human medicinal product for use in a minor species or for a minor use

In the EU, through the cascade system, human medicines are widely used to treat minor species and for minor uses in major species (such as cats and dogs). Whilst in some cases the strength and dosage forms may not be ideal for such use, often Veterinary Surgeons have found practical and acceptable ways to accurately administer the medicine to animals.

It must be acknowledged that there may be some situations where a human pharmaceutical product could not be authorised for use in animals. This will particularly be the case when considering unit dose products intended for use in a lower bodyweight minor species. Crushing and dilution of tablets/capsules cannot be condoned. Equally dilution of injections cannot be supported. However, steps such as: the use of syringes designed to measure very low volumes of an injection (for example those more usually used to administer insulin); use of scored tablets; dilution of oral or topical solutions, can be acceptable. Where a dilution step is required, suitable diluents and evidence of compatibility and stability will need to be addressed.

[1] This will require amendment to Annex I of Directive 2001/82/EC.

If a human medicine is already authorised in the EU and has been assessed for conformance with the current legislation, an acceptable quality dossier already exists for the product. If it is confirmed that the proposed MUMS product is identical to an EU authorised human medicine with the exception of the labelling of the product and any administration devices supplied with the product, then the assessment of the core quality data will **not** be repeated by the Veterinary Regulatory Authority. The only exception to this would be where the minor species was a food producing species. In such cases an assessment could be undertaken by the Veterinary Regulatory Authority but only fundamental issues should be pursued with the Applicant. The qualification of impurities is one such possible area, for example, where the human medicine is used acutely but the veterinary medicine would be administered to a food producing species over a long period of time (that is, as a chronic treatment). The supporting quality data which would be routinely assessed would be those dealing with the use of the product in the minor species or for the minor use, i.e. dosing accuracy and in-use studies.

In order to progress such an application, the administrative data required in addition to that in Part I of the dossier, and the quality data required would be as follows:

1. The Marketing Authorisation number of the human medicine.
2. The name of the member state in which the human medicine is authorised and the date this authorisation was issued.
3. The current agreed SPC for the authorised human medicine.
4. The complete formula of the human medicine.
5. A letter from the Marketing Authorisation holder of the human medicine confirming that they have either, supplied the Applicant with all of the necessary data and know-how to allow them to manufacture a product identical to the human medicine, or, that they will be supplying product directly to the Applicant that is of identical quality to the authorised human medicine.
6. A full copy of the quality part of the dossier as submitted to the relevant human Regulatory Authority with the initial application, taking account of any responses to questions and subsequent changes. This would be acceptable in the Common Technical Document (CTD) format[2].
7. An additional TSE risk assessment if the product is to be used in a species susceptible to TSEs, for example, goats.
8. A brief paper considering how the correct dose will be measured and administered in practise for the proposed target species/indication, together with a justification for the proposed SPC statements designed to help ensure accuracy of dosing.
9. Supplementary in-use studies as appropriate.

Items 1 to 5 are required to check that the proposed product is indeed identical to the EU authorised human medicine.

Item 6 will not be assessed, unless checks reveal that the proposed MUMS product differs from the human authorised product or the minor species is a food producing species and then only fundamental issues will be considered.

Items 7 to 9 will be assessed.

In the case of variations to the authorised MUMS product, systematic variation applications with supporting data will be required. However, evidence of approval of a variation by a Human Regulatory Authority will mean that no additional assessment will be undertaken on core quality issues by the Veterinary Regulatory Authority.

[2] This will require amendment to Annex I of Directive 2001/82/EC.

4.4 Entirely new medicine for use in a minor species or for a minor use

Due to the costs of developing an entirely new medicine, it is considered that this category will only be encountered very rarely. Furthermore, the active substances in such medicines are likely to be substances that are: used in human medicines, have been previously authorised in a veterinary medicine or are used as pesticides. In such cases, a full supporting quality data package will be required. Applicants are advised to routinely request Scientific Advice for such applications. The following are examples of the areas in which the data requirements might be reduced, depending upon the active substance and the dosage form:

Active substance batch analysis data

- Data required for 2 pilot batches only.

Active substance stability

- For all active substances (i.e. pharmacopoeial and non-pharmacopoeial) formal stability studies according to CVMP guidelines are not required if testing to full specification immediately before manufacture of the final product is proposed.

Final product process validation data

- For standard and non-standard [3]processes, for full scale batches, provision of a process validation scheme only. Thus permitting process validation studies to be conducted on full scale batches post authorisation*. Final reports from such process validation studies are to be available for scrutiny during GMP inspections. However, the Licensing Authority must be informed if problems are encountered on validation of the process at the full scale, together with the proposed action.

  * Process development and validation data should be included in the dossier pre-authorisation as necessary in accordance with the normal requirements set out in the guideline on process validation.

Final product batch analysis data

- Data required for 2 pilot batches only.
- Commitment to be given to inform the Regulatory Authorities immediately if any of the first three production batches fail to meet the agreed Finished Product Specification and to submit these batch analyses data together with the proposed action.

Final product stability

- Data required in application for two pilot batches only.
- First 2 production batches (usually post authorisation) to be subjected to stability testing.
- Concept of bracketing/matrixing to be applied.
- Photostability data not required as long as the product is provided in a carton (or other suitable protective packaging) and is labelled “protect from light”.

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

- The Rules Governing Medicinal Products in the EU: Volume 7B “Immunologicals and quality”

[3] This will require amendment to Annex I of Directive 2001/82/EC.

- 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 and CVMP/CHMP quality guidelines
- VICH quality guidelines