EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 January 2016
EMA/CVMP/QWP/128710/2004-Rev.1
Committee for Medicinal Products for Veterinary Use (CVMP)

Guideline on quality data requirements for veterinary medicinal products intended for minor use or minor species (MUMS)/limited market

Draft

Adopted by CVMP	July 2006
Revised draft agreed by Quality Working Party	December 2015
Adopted by CVMP for release for consultation	21 January 2016
Start of public consultation	3 February 2016
End of consultation (deadline for comments)	31 July 2016

This guideline updates the CVMP Guideline on quality data requirements for veterinary medicinal products intended for minor uses or minor species / limited market (EMEA/CVMP/QWP/128710/2004).

Comments should be provided using this template. The completed comments form should be sent to vet-guidelines@ema.europa.eu

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Guideline on quality data requirements for veterinary medicinal products intended for minor use or minor species (MUMS)/limited market

Table of contents

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 the 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 quality 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 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.

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

- Extension of/variation to an existing veterinary medicinal product for use in a minor species.
- Variation to an existing veterinary medicinal product for a minor use/limited market.
- Existing human medicinal product for use in a minor species or for a minor use/limited market.
- Entirely new medicine for use in a minor species or for a minor use/limited market.

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.

As a general principle, the CVMP, joint CVMP/CHMP and VICH guidelines concerning quality 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:

"(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

[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*).

be applicable. In such cases, relevant scientific guidelines and/or scientific advice should be taken into account."

5. Specific requirements for each of the different categories of applications for minor uses and minor species

5.1. Extension of/variation to an 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, 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 cannot 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, dosage form or route of administration, 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[2] 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 competent authority(ies) 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 for 2 pilot batches only.
- Commitment to be given to inform the competent authority(ies) 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.

5.2. Variation to an existing veterinary medicinal product for a minor use/limited market

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. A supplement

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

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 should be supplied.

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.

5.3. Existing human medicinal product for use in a minor species or for a minor use/limited market

In the EU, through the cascade system, human medicines are widely used to treat minor species and for minor use 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.

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 competent authority(ies). 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 competent authority(ies) 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[3]. This would be acceptable in the Common Technical Document (CTD) format.

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.

10. If the finished product manufacturing site for the veterinary product is different from that for the human product, for standard and non-standard[4] processes batch data from 2 pilot scale batches is required. In addition, 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 competent authority(ies) must be informed if problems are encountered on validation of the process at the full scale, together with the proposed action(s).

    * 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.

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.

Items 7 to 10 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 competent authority(ies).

5.4. Entirely new medicine for use in a minor species or for a minor use/limited market

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.

[3] This is necessary because Veterinary competent authorities will not hold a copy of the dossier for the human medicinal product.
[4] This will require amendment to Annex I of Directive 2001/82/EC.

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. However, there might still be a need for some stress testing to investigate the degradation profile of non-pharmacopoeial substances and to check the stability-indicating characteristics of the control method.

Final product process validation data

- For standard and non-standard[5] 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 competent authority(ies) 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 competent authority(ies) 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:

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 quality guidelines. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000191.jsp&mid=WC0b01ac058002dd30

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