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

Draft

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This guideline updates the CVMP Guideline on data requirements for immunological veterinary medicinal products intended for minor use or minor species / limited markets (EMA/CVMP/IWP/123243/2006-Rev.2).

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Guideline on data requirements for immunological 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 immunological 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.

Specific clarifications are provided in the appropriate sections of the guideline.

The general aim of this guideline is to define acceptable data requirements for the demonstration of quality, safety and efficacy for immunological veterinary medicinal products (IVMPs) intended for MUMS/limited market. In this context, data requirements for the demonstration of quality, safety and efficacy will be influenced to a certain extent by the characteristics of the product and its intended use.

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

The objective of this guideline is to clarify the requirements for the following applications in accordance with the EMA MUMS/limited market policy and guidance (EMA/308411/2014, EMA/CVMP/388694/2014):

- new applications for marketing authorisations of immunological veterinary medicinal products classified as MUMS/limited market.
- line extension and variation applications to an existing MUMS product,
- line extension and variation applications to an existing product authorised for a major indication in a major species where the line extension/variation is classified as MUMS/limited market.

The guideline covers vaccines and immunosera. However, other immunological products may fall under the MUMS/limited market policy and reduction in data requirements may apply but for such products specific scientific advice should be sought. For GMO and DNA vaccines this guideline is only applicable for efficacy requirements. If the vaccine contains a genetically modified organism (GMO) according to Directive 2001/18/EC, the full set of data with regard to Directive 2001/18/EC should be provided.

For all other vaccines it is acceptable to submit data generated for other vaccines containing the same active ingredient(s) and adjuvant(s) which are already authorised to fulfil relevant parts of the quality, safety and efficacy data requirements of Annex I to 2001/82/EC. Furthermore, it is acceptable for an applicant to submit data which has been gained with similar GMO constructs already authorised to fulfil part of the requirements for quality and safety.

Horses are considered as a minor species; however, for some IVMPs, e.g. equine influenza vaccines, where the use is normally not minor or considered a limited market, the reduced data requirements according to this guideline may not be applicable.

This guideline does not cover IVMPs for diseases subject to European Union control, where vaccination is only allowed under emergency conditions (e.g. Foot-and-Mouth Disease, Classical Swine Fever or avian influenza), based on decisions of the relevant EU bodies and where guidelines, specific for these products, apply (see the guidance document on the classification of veterinary medicinal products indicated for minor use minor species (MUMS)/limited market (EMA/CVMP/388694/2014).

As a general principle, the CVMP and VICH guidelines concerning immunologicals 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.

[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*).

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

5. Requirements for immunological veterinary medicinal products for minor use/limited market

Generally, the requirements as mentioned in Title II of Annex I to Directive 2001/82/EC and the relevant European Pharmacopoeia (Ph. Eur.) general chapters and monographs apply to all immunological veterinary medicinal products, including those for MUMS/limited market. However, some reductions in requirements for new marketing authorisations and line extensions could be acceptable and these are listed in Table 1. For line extensions to add a minor species no additional quality data are required. Where applicable, Table 1 is also relevant for variations.

In addition to the data reductions listed in Table 1, the following general considerations regarding reductions in requirements can be applied:

- For laboratory trials, the GLP requirements could be lifted, if appropriately justified.
- Literature may be used to demonstrate the safety and efficacy warnings and indications, provided these data were generated using the product for which the application is made. Bibliographic data should preferably originate from acknowledged scientific literature ideally from peer-reviewed journals.
- It is recognised that existing field studies may not always satisfy current GCP requirements. Such studies may be considered acceptable if the design is appropriate to the stated objective of the study.
- The applicant should test for treatment differences using appropriate statistical methodology. It should be possible in all cases to demonstrate a benefit of treatment that is statistically significant. However, the practical limitations of data collection for a minor use/limited market product will be taken into consideration.

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. Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC http://eur-lex.europa.eu/resource.html?uri=cellar:303dd4fa-07a8-4d20-86a8-0baaf0518d22.0004.02/DOC_1&format=PDF

4. CVMP and VICH guidelines for immunologicals http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000374.jsp&mid=WC0b01ac058002ddc5

Table 1: Reduced data requirements for IVMPs classified as MUMS/limited market

Please note that the numbering of the table refers to the numbering in Title II of Annex I to Directive 2001/82/EC, as amended by Directive 2009/9/EC.

No. of section	Section title	Reduced data requirements	Applications for new Marketing Authorisations		Line extension	
			Live	Inactiv.	Live	Inactiv.
1. SUMMARY OF THE DOSSIER						
1.C	DETAILED AND CRITICAL SUMMARIES (DACS)	A separate DACS for each section of the dossier is not required. A single DACS covering quality, safety and efficacy evaluating any data gaps in the dossier and demonstrating that the product is of adequate quality and safety, and that the claims are supported, taking account of the risks and benefits of the product, is acceptable.	✔	✔	✔	✔
2. CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL/MICROBIOLOGICAL INFORMATION (QUALITY)						
2.B	DESCRIPTION OF MANUFACTURING METHOD	Use of 2 pilot batches to validate the consistency of production process for the finished product is acceptable (to be verified with a 3rd batch at industrial scale as a post-authorisation commitment).	✔	✔	N/a	N/a
2.C.2.1	PRODUCTION AND CONTROL OF STARTING MATERIALS: Starting materials of biological origin	For all Master seeds and immunosera: Extraneous agents testing: only for those agents that may occur in the source species.	✔	✔	N/a	N/a
2.E.7	CONTROL TEST ON THE FINISHED PRODUCT: Sterility and purity test	Extraneous agents testing: permitted to be done on final bulk.	✔	✔	N/a	N/a

No. of section	Section title	Reduced data requirements	Applications for new Marketing Authorisations		Line extension	
			Live	Inactiv.	Live	Inactiv.
2.F	BATCH-TO-BATCH CONSISTENCY	Use of 2 pilot batches is acceptable (to be verified at industrial scale with a 3rd batch as a post-authorisation commitment).	✔	✔	N/a	N/a
2.G	STABILITY TESTS	Results of 1 pilot batch are acceptable (results of one industrial batch to be provided as a post-authorisation commitment).	✔	✔	N/a	N/a
		Stability data for each final container type should be provided but stability data on one final container size is acceptable provided the presentation is the largest one.	✔	✔	N/a	N/a
		Stability data obtained with combined products can be used for smaller combinations or single products derived thereof as final data.	✔	✔	N/a	N/a
		In-use-shelf life data can be subject to a post authorisation commitment.	✔	✔	N/a	N/a
3. SAFETY TESTS						
3.B	LABORATORY TESTS	Laboratory safety studies for inactivated vaccines may be combined with laboratory efficacy studies and therefore standard batches may be used with no requirement to demonstrate the safety with batches formulated with maximum antigen content.	N/a	✔	N/a	✔
		For live vaccines no passage requirement. The maximum titre should be adequately justified.	✔	N/a	✔	N/a
3.B.1	Safety of the administration of one	Not needed if overdose test is provided.	✔	N/a	✔	N/a
3.B.3	Repeated dose administration	Safety of the primary vaccination schedule to be demonstrated.	✔	✔	✔	✔

No. of section	Section title	Reduced data requirements	Applications for new Marketing Authorisations		Line extension	
			Live	Inactiv.	Live	Inactiv.
3.B.4 and 5	Examination of reproductive performance and immunological functions	Studies for the examination of reproductive performance and immunological functions may be omitted. If such studies are not performed, relevant warnings should be given in the SPC.	✔	✔	✔	✔
3.B.6.1	Spread of vaccine strain	Published literature may be used to fulfil this requirement. In the absence of adequate scientific literature the relevant studies should be performed to evaluate spread to unvaccinated target animals and potentially non-target species.	✔	N/a	✔	N/a
3.B.6.2	Dissemination in the vaccinated animal	Data not required unless the vaccine strain is shown to spread. Published literature may be used to fulfil this requirement. In the absence of adequate scientific literature the relevant studies should be provided.	✔	N/a	✔	N/a
		Dissemination studies are required in all cases for zoonotic diseases and take into account the persistence of the organism at the injection site.	✔	N/a	✔	N/a
3.C	FIELD STUDIES	If laboratory studies adequately demonstrate the absence of a safety risk, field studies are not required. It should be adequately demonstrated that the data from the laboratory studies are representative for safety under field conditions. Safety data from the field may still be required as a post-authorisation commitment.	✔	✔	✔	✔
4. EFFICACY TESTS						
4.B	Laboratory trials	For inactivated vaccines may be combined with laboratory safety studies.	N/a	✔	N/a	✔

No. of section	Section title	Reduced data requirements	Applications for new Marketing Authorisations		Line extension	
			Live	Inactiv.	Live	Inactiv.
		For live vaccines no passage requirement. The minimum titre should be adequately justified.	✔	N/a	✔	N/a
		For immunosera an immunological action should be demonstrated.	N/a	N/a	N/a	N/a
		For line extensions, omission of studies such as duration of immunity, effect of MDA, are acceptable, provided that it is made clear in the SPC that the data are not available.	N/a	N/a	✔	✔
4.C	Field trials	Field studies are not required if the laboratory efficacy studies adequately demonstrate that the studies are representative of efficacy under field conditions.	✔	✔	✔	✔
		Field efficacy studies may replace laboratory efficacy studies, if adequately justified.	✔	✔	✔	✔

205 N/a = not applicable