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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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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 a guideline on data requirements for MUMS/limited market for immunological veterinary medicinal products (IVMPs). This guideline is 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 such products, and ultimately leading to an increased availability of IVMPs.

This MUMS guideline has 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 these data requirements. This guideline describes the data requirements regarding IVMPs classified as MUMS/limited market.

This guideline also presents opportunities to waive animal testing requirements for veterinary medicines intended for MUMS/limited market, which is in line with the recent implementation of Directive 2010/63/EC regarding the protection of animals used for experimental and other scientific purposes and the 3Rs principles of replacement, reduction and refinement.

1. Introduction

Concern has been expressed by parties involved in 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 MUMS/limited market will improve both animal welfare and animal health as well as in some cases, public health. The Agency began discussions and consultations on this issue in 1998 and, since that time, the CVMP is active in initiatives to address the lack of veterinary medicines in this field.

The Agency policy for classification and incentives for veterinary medicinal products indicated for MUMS/limited markets (EMA/308411/2014) 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. An additional benefit of this policy is that it presents opportunities to reduce animal testing requirements, which is in line with the 3R principles of replacement, reduction and refinement.

These guidelines are intended to reduce data requirements where possible for products classified as MUMS/limited market while providing assurance of appropriate quality, safety and efficacy and complying with the current 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.

The general aim of this guideline is to define acceptable data requirements for the demonstration of quality, safety and efficacy for IVMPs classified as 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.

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

The guidance provided in this document is general. In addition, Scientific Advice is available upon request to confirm precise requirements for a specific application.

2. Scope

The objective of this guideline is to clarify the data requirements for the following applications in accordance with the 'Revised policy for classification and incentives for veterinary medicinal products indicated for minor use minor species (MUMS)/limited market' (EMA/308411/2014) and 'Guidance on the classification of veterinary medicinal products indicated for minor use minor species (MUMS)/limited market' (EMA/CVMP/388694/2014):

- New applications for marketing authorisations of IVMPs classified as MUMS/limited market.
- Line extension and variation applications to authorised IVMPs classified as MUMS/limited market IVMP.
- Line extension and variation applications to an existing IVMP authorised for a major indication in a major species where the line extension/variation is classified as MUMS/limited market.

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.

This guideline is not intended to provide information on administrative procedures (including scientific advice procedures) or the possible reduction/deletion of fees for these procedures.

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]

[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).

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 II for immunologicals.

One of the intentions of the current legislation for the authorisation of veterinary medicines as laid down in the preambles of Directive 2001/82/EC and 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 IVMPs 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 IVMPs, including those for MUMS/limited market. The CVMP guidelines concerning IVMPs (e.g. association guideline, in use stability guideline) are applicable to MUMS/limited market products. Possible reductions in requirements for new marketing authorisations and line extensions listed in Table 1. Where applicable, Table 1 is also relevant for variations.

For IVMPs that do not contain a GMO it is acceptable to submit data generated for other IVMPs 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 Directive 2001/82/EC.

For IVMPs containing a GMO this guideline is only applicable for quality and efficacy requirements. In addition to requirements of Directive 2001/18/EC, the full set of safety data as required in Directive 2001/82/EC should be provided. Nevertheless it is acceptable for an applicant to submit data which has been generated for similar GMO constructs already authorised to fulfil part of the requirements for quality and safety.

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 can be lifted provided the protocols and reports allow a satisfactory assessment of the trials.
- Literature may be used to support the safety and efficacy warnings and indications, provided these data were generated using the product for which the application is made. Bibliographic data should originate from acknowledged scientific literature ideally from peer-reviewed journals.
- Field trials are required when sufficient data from laboratory studies are not provided to validate efficacy. Such studies may not need to be conducted to current GCP requirements, provided the protocols and reports allow a satisfactory assessment of the trials.
- The applicant should test for treatment differences using appropriate statistical methodology. It should be possible in all cases to demonstrate a benefit of treatment. 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.

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 short DACS covering quality, safety and efficacy evaluating and justifying any data gaps in the dossier is sufficient. A benefit-risk assessment should confirm adequate quality and safety, and support the proposed indications.	✔	✔	✔	✔
2. CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL/MICROBIOLOGICAL INFORMATION (QUALITY)						
2.B	DESCRIPTION OF MANUFACTURING METHOD	Use of 2 pilot/R&D[2] 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] Pilot batch: small scale industrial batch, but in full compliance with the production process described in the licensing dossier.
R&D batch: batch produced under laboratory conditions but in full compliance with the production process described in the licensing dossier

No. of section	Section title	Reduced data requirements	Applications for new Marketing Authorisations		Line extension	
			Live	Inactiv.	Live	Inactiv.
2.E.7	CONTROL TEST ON THE FINISHED PRODUCT: Sterility and purity test	Extraneous agents testing: permitted to be done on either final bulk or on the individual antigen bulk.	✔	✔	N/a	N/a
2.F	BATCH-TO-BATCH CONSISTENCY	Use of 2 pilot/R&D 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/R&D batch is 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 selected presentation is justified by the applicant.	✔	✔	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
		When in-use-shelf life is necessary, if it can be provisionally based on experience with other vaccines, the 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 IVMPs 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. Data from larger combinations are acceptable.	N/a	✔	N/a	✔
		For live IVMPs no passage requirement. The maximum titre should be adequately justified.	✔	N/a	✔	N/a

No. of section	Section title	Reduced data requirements	Applications for new Marketing Authorisations		Line extension	
			Live	Inactiv.	Live	Inactiv.
3.B.1	Safety of the administration of one dose	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.	✔	✔	✔	✔
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 should take into account the persistence of the organism at the injection site.	✔	N/a	✔	N/a

No. of section	Section title	Reduced data requirements	Applications for new Marketing Authorisations		Line extension	
			Live	Inactiv.	Live	Inactiv.
3.C	FIELD STUDIES	If laboratory studies adequately demonstrate the absence of a significant target animal safety risk, field studies are not required. It should be adequately justified that the data from the laboratory studies are representative for safety under field conditions. Appropriate justification includes the use of representative animals versus field conditions in the EU, e.g. body weight, physiological status and reproduction performance. Safety data from the field may still be required as a post-authorisation commitment. Data from larger combinations are acceptable.	✔	✔	✔	✔
4. EFFICACY TESTS						
4.B	Laboratory trials	For inactivated IVMPs may be combined with laboratory safety studies. Data from larger combinations are acceptable if justified.	N/a	✔	N/a	✔
		For live IVMPs no passage requirement. The minimum titre should be adequately justified. Data from larger combinations are acceptable if justified.	✔	N/a	✔	N/a
		For immunosera an immunological action should be demonstrated.	N/a	N/a	N/a	N/a
		Omission of studies such as duration of immunity is acceptable, provided that it is made clear in the SPC that the data are not available and a commitment to perform the DOI study post-authorisation is made unless justified. Omission of studies such as effect of MDA, are acceptable, provided that it is made clear in the SPC that the data are not available. Data from larger combinations are acceptable if justified.	N/a	N/a	✔	✔

No. of section	Section title	Reduced data requirements	Applications for new Marketing Authorisations		Line extension	
			Live	Inactiv.	Live	Inactiv.
4.C	Field trials	Field studies are not required if the laboratory efficacy studies adequately establish and validate the efficacy and it is justified that they are representative of efficacy under field conditions. Appropriate justification includes the use of a laboratory challenge model which has been shown to be relevant to EU field situation and reproducing relevant clinical signs and / or microbiological outcomes. Data from larger combinations are acceptable if justified.	✔	✔	✔	✔
		Field efficacy studies may replace laboratory efficacy studies, if adequately justified. Data from larger combinations are acceptable if justified.	✔	✔	✔	✔

3 N/a = not applicable