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Guideline on data requirements for applications for immunological veterinary medicinal products intended for limited markets submitted under Article 23 of Regulation (EU) 2019/6

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This guideline replaces the Guideline on data requirements for immunological veterinary medicinal products intended for minor uses or minor species (MUMS)/limited market (EMA/CVMP/IWP/123243/2006-Rev.3).

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Official address Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands

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Executive summary

Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC introduces specific provisions for applications for limited markets (Article 23).

The general aim of this guideline is to define acceptable data requirements for the demonstration of safety and efficacy in case of marketing authorisation applications for immunological veterinary medicinal products (IVMPs) intended for limited markets submitted under Article 23 of Regulation (EU) 2019/6.

It is the intention of the guideline to indicate which data requirements can be reduced for this type of applications; however, it is recognised that this is not always feasible as not all scenarios can be addressed in a general guidance document.

The specific data requirements for the demonstration of safety and efficacy for immunological veterinary medicinal products intended for limited markets submitted under Article 23 of Regulation (EU) 2019/6 are presented in Table 1 of the guideline.

1. Introduction

From 2007 to 2017, the CVMP developed a guideline on data requirements for MUMS/limited market for immunological veterinary medicinal products with the aim to stimulate research, development and innovation of new veterinary medicines intended for minor uses and minor species (MUMS/limited market). That guideline was developed with the purpose of reducing data requirements where possible for products classified as intended for 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.

Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products repealing Directive 2001/82/EC introduces specific provisions for limited markets including definition of limited market and specific conditions for granting derogation to the data requirements defined in Annex II of the Regulation. These provisions need to be taken into account when defining the data requirements.

Therefore, the former MUMS/limited markets guidelines have been replaced by the current limited markets guidelines, which were drafted in line with the new legal provisions.

It is the intention of the guideline to provide data requirements that can be reduced in accordance with Article 23 of Regulation (EU) 2019/6, to facilitate the applicant's work for estimating the required resources for a limited market application preparing the application dossier and provide for predictability. However, it is recognised that this is not always feasible as not all 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 safety and efficacy for IVMPs for limited markets.

In addition, the reduced data requirements for limited markets will result in certain cases in the reduction of the number of animals used in testing, which is in line with the Directive 2010/63/EU on the protection of animals used for scientific purposes and the 3Rs principles of replacement, reduction and refinement.

The guidance provided in this document is general. However, if during product development, an applicant wishes to have clarity on precise data requirements for an application relating to a specific VMP, Scientific Advice is available upon request.

2. Scope

This guideline applies to marketing authorisation applications for immunological veterinary medicinal products intended for limited markets.

The objective of this guideline is to clarify the data requirements for applications for limited markets and thereby provide applicants with information on safety and efficacy data requirements to support applications for authorisation of immunological veterinary medicinal products under Article 23 of Regulation (EU) 2019/6.

According to Annex II to Regulation (EU) 2019/6, a novel therapy veterinary medicinal product could also fall into the category of immunological veterinary medicinal products. This guideline also applies to these cases.

Biological veterinary medicinal products other than immunological veterinary medicinal products are out of the scope of this guideline. Data requirements for these products are discussed in the specific revised guidelines on efficacy and target animal safety and on safety and residue data requirements for veterinary medicinal products intended for limited markets.

All pre-clinical in vivo studies conducted by an applicant to support an application for marketing authorisation should be in accordance with the requirements of Directive 2010/63/EU on the protection of animals used for scientific purposes and the 3Rs principles of replacement, reduction and refinement (EMA/CHMP/CVMP/JEG-3Rs/450091/2012; EMA/CHMP/CVMP/3Rs/164002/2016).

This guideline is not intended to provide information on administrative procedures (including scientific advice procedures).

3. Definitions

Definitions are provided in Article 4 of Regulation (EU) 2019/6:

Limited market

According to Article 4(29) of Regulation (EU) 2019/6, '*Limited market*' means a market for one of the following medicinal product types:

- (a) *veterinary medicinal products for the treatment or prevention of diseases that occur infrequently or in limited geographical areas;*
- (b) *veterinary medicinal products for animal species other than cattle, sheep for meat production, pigs, chickens, dogs and cats.*

Details on applications for limited markets, on the validity of a marketing authorisation for a limited market and procedure for its re-examination are laid down in Articles 23 and 24 of the above-mentioned regulation.

Immunological veterinary medicinal product

According to Article 4(5) of Regulation (EU) 2019/6 an '*Immunological veterinary medicinal product*' means a *veterinary medicinal product intended to be administered to an animal in order to produce active or passive immunity or to diagnose its state of immunity;*

Clinical trial

According to Article 4(17) of Regulation (EU) 2019/6, a '*Clinical trial*' is a study which aims to examine under field conditions the safety or efficacy of a veterinary medicinal product under normal conditions of animal husbandry or as part of normal veterinary practice for the purpose of obtaining a marketing authorisation or a change thereof.

Pre-clinical study

According to Article 4(18) of Regulation (EU) 2019/6, a '*Pre-clinical study*' means a study not covered by the definition of clinical trial which aims to investigate the safety or efficacy of a veterinary medicinal product for the purpose of obtaining a marketing authorisation or a change thereof.

4. Legal basis

Requirements for a marketing authorisation application are laid down in Article 8(1)(b) of Regulation (EU) 2019/6 and are specified in Annex II of Regulation (EU) 2019/6, section IIIb for immunological veterinary medicinal products.

One of the intentions of the current legislation for the authorisation of veterinary medicines as laid down in the preambles of Regulation (EU) 2019/6, recital no. 30, is to facilitate the authorisation of veterinary medicinal products intended for limited markets:

"(30) Companies have less interest in developing veterinary medicinal products for markets of a limited size. In order to promote the availability of veterinary medicinal products within the Union for those markets, in some cases it should be possible to grant marketing authorisations without a complete application dossier having been submitted, on the basis of a benefit-risk assessment of the situation and, where necessary, subject to specific obligations. In particular, the grant of such marketing authorisations should be possible in the case of veterinary medicinal products for use in minor species or for the treatment or prevention of diseases that occur infrequently or in limited geographical areas."

In addition, Article 23 of Regulation (EU) 2019/6 introduces a specific legal basis for veterinary medicinal products intended for limited markets, also specifying the conditions, which need to be fulfilled by applications for limited markets:

"1. By way of derogation from point (b) of Article 8(1), the applicant shall not be required to provide the comprehensive safety or efficacy documentation required in accordance with Annex II, if all of the following conditions are met:

(a) the benefit of the availability on the market of the veterinary medicinal product to the animal or public health outweighs the risk inherent in the fact that certain documentation has not been provided;

(b) the applicant provides the evidence that the veterinary medicinal product is intended for a limited market.

2. Where a veterinary medicinal product has been granted a marketing authorisation in accordance with this Article, the summary of product characteristics shall clearly state that only a limited assessment of safety or efficacy has been conducted due to the lack of comprehensive safety or efficacy data."

This is also reflected in Annex II of Regulation (EU) 2019/6 under section IV.6 – *Applications for limited markets*:

"A marketing authorisation may be granted for a limited market in the absence of comprehensive safety and/or efficacy data when, as provided for in Article 23 of this Regulation, the applicant

demonstrates that the product is intended for use in a limited market and that the benefit of availability of the new product outweighs the risk associated with the omission of some of the safety or efficacy data required by this Annex.

For such applications, the applicant shall submit Parts 1 and 2 as described in this Annex.

For Parts 3 and 4, some of the safety or efficacy data required by this Annex may be omitted. As regards the extent of safety and efficacy data that may be omitted, the relevant guidance published by the Agency shall be taken into account."

5. Requirements for IVMPs for limited markets

Generally, the requirements as mentioned in section IIIb of Annex II to Regulation (EU) 2019/6 and the relevant European Pharmacopoeia (Ph. Eur.) general chapters and monographs apply to all IVMPs, including those for limited markets. The CVMP guidelines concerning IVMPs (e.g. association guideline, in-use stability guideline) are applicable to products for limited market products. Possible reductions in requirements for new marketing authorisations and relevant variations (such as variations to add new target species) are listed in Table 1.

For IVMPs that do not contain a GMO, it is acceptable to submit data generated for other IVMPs, which are already authorised in the EU for the same target species and which containing the same active ingredient(s) and adjuvant(s). Extrapolation of data from one target species (approved for IVMPs authorised in the EU and which contain the same active ingredient(s) and adjuvant(s)) to another target species is also acceptable, pending appropriate justifications.

For IVMPs containing a GMO, this guideline is applicable for efficacy requirements. For safety, the requirements of Directive 2001/18/EC must be met. In line with the latter Directive, 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 safety.

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

1. For pre-clinical safety studies (laboratory safety studies), the GLP requirements can be lifted provided the protocols and reports allow a satisfactory assessment of the trials.
2. In case of data gaps, 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 (e.g. for different categories of the target species). Bibliographic data should originate from acknowledged scientific literature ideally from peer-reviewed journals.
3. Clinical trials (field trials) are required when sufficient data from laboratory (pre-clinical) studies are not provided to validate safety and/or 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.
4. The applicant should test for treatment differences between vaccinated and control animals 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 limited market product will be taken into consideration.

6. Summary of Product Characteristics

Where a veterinary medicinal product has been granted a marketing authorisation in accordance with Article 23 of Regulation (EU) 2019/6, the summary of product characteristics shall clearly state that only a limited assessment of safety or efficacy has been conducted due to the lack of comprehensive safety or efficacy data. In line with Article 35(1)(j)(i) of Regulation (EU) 2019/6, the SPC will carry the following statement: "*marketing authorisation granted for a limited market and therefore assessment based on customised requirements for documentation*".

In general, the QRD veterinary annotated product information template is also applicable for veterinary medicinal product granted a marketing authorisation in accordance with Article 23. Standard statements, given in the template should be used whenever they are applicable. This concerns the SPC, the labelling and the package leaflet.

Details on the data which have not been provided by the applicant (i.e. the data gaps) will be included and made publicly available in the European public assessment report.

References

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

1. Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC
<https://eur-lex.europa.eu/eli/reg/2019/6/oj>
2. 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 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
3. Commission Delegated Regulation (EU) 2021/805 of 8 March 2021 amending Annex II to Regulation (EU) 2019/6 of the European Parliament and of the Council
<https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32021R0805&from=EN>
4. Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes
5. <https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:276:0033:0079:en:PDF>
6. Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches (EMA/CHMP/CVMP/JEG-3Rs/450091/2012)
7. Reflection paper providing an overview of the current regulatory testing requirements for veterinary medicinal products and opportunities for implementation of the 3Rs (EMA/CHMP/CVMP/3Rs/164002/2016)
8. Reflection paper on classification of a product as intended for a limited market according to Article 4(29) and/or eligibility for authorisation according to Article 23 (Applications for limited markets) (EMA/CVMP/235292/2020)

Annex 1: Reduced data requirements for IVMPs intended for limited markets

Please note that the numbering of the table refers to the numbering in Section IIIb of Annex II to Regulation (EU) 2019/6.

No. of section	Section title	Reduced data requirements	Applications for new Marketing Authorisations and relevant variations	
			Live	Inactivated
3.A	General requirements	For inactivated IVMPs, use of standard batches (no maximum antigen content necessary) in safety studies is allowed. The safety and efficacy studies may be combined in the same pre-clinical (laboratory) study, using the same batch(es) of an IVMP.	N/a	✓
		For live IVMPs, the use of the least attenuated passage level is not required. The titre used in the studies should be adequately justified.	✓	N/a
		For both live and inactivated IVMPs, data from larger combinations are acceptable, if justified.	✓	✓
		The use of pilot/R&D batches is possible.	✓	✓
3.B	Pre-clinical studies (Laboratory safety studies)			
3.B.2	Safety of one administration of an overdose	Safety of an overdose is not required.	✓	N/a
3.B.3	Safety of the repeated administration of one dose	Safety of first re-vaccination is not required. Demonstration of safety of the primary vaccination schedule is sufficient.	✓	✓
3.B.4	Examination of reproductive performance	Studies for the examination of reproductive performance may be omitted. If such studies are not performed, relevant warnings should be given in the SPC.	✓	✓
3.B.5	Examination of immunological functions	Studies for the examination of immunological functions may be omitted. If necessary, relevant warnings should be given in the SPC.	✓	✓

No. of section	Section title	Reduced data requirements	Applications for new Marketing Authorisations and relevant variations	
			Live	Inactivated
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 which could be highly susceptible to the vaccine strain.	✓	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
		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
3.C	Clinical trials (field studies)	<p>If pre-clinical (laboratory) studies adequately demonstrate the absence of a significant target animal safety risk, clinical (field) studies are not required.</p> <p>It should be adequately justified that the data from the pre-clinical (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.</p>	✓	✓
4.A	General requirements	For inactivated IVMPs, use of standard batches (no minimum antigen content necessary) in efficacy studies is allowed. The safety and efficacy studies may be combined in the same pre-clinical (laboratory) study, using the same batch(es) of an IVMP.	N/a	✓
		For both live and inactivated IVMPs, data from larger combinations are acceptable, if justified.	✓	✓
		The use of pilot/R&D batches is possible.	✓	✓

No. of section	Section title	Reduced data requirements	Applications for new Marketing Authorisations and relevant variations	
			Live	Inactivated
4.B	Pre-clinical studies (Laboratory trials)			
		For live IVMPs, the efficacy studies may be combined with one-dose pre-clinical (laboratory) safety studies. The use of the maximum passage level is not required. The titre used in the studies should be adequately justified.	✓	N/a
		For immunosera, an immunological action should be demonstrated. Where suitable published data exist on protective antibody levels, a reference could be made and challenge studies could be avoided	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.	✓	✓
		Omission of studies such as effect of maternally derived antibodies (MDA), are acceptable, provided that it is made clear in the SPC that the data are not available, and it should be scientifically justified.	✓	✓
4.C	Clinical trials (Field trials)	Clinical (field) studies are not required if the pre-clinical (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.	✓	✓
		Where laboratory trials cannot be supportive of efficacy, the performance of field trials alone may be acceptable.	✓	✓

N/a = not applicable

Relevant variations: such as variations to add new target species