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Guideline on safety and efficacy data requirements for applications for immunological veterinary medicinal products intended for limited markets but not eligible for authorisation under Article 23 of Regulation (EU) 2019/6

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Table of contents

Executive summary

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 (the Regulation) introduced specific provisions for limited markets. Article 4(29) of the Regulation provides a definition for limited market and Article 23 provides specific derogations on the submission of safety and efficacy data when certain conditions applicable to marketing authorisation applications for limited markets are met.

The purpose of this scientific guidance is to indicate how the general flexibilities provided within Annex II can be applied to immunological veterinary medicinal products for limited markets as defined by Article 4(29) of the Regulation due to the characteristics of these products. Specifically, this guideline clarifies the data requirements for the demonstration of safety and efficacy for applications for immunological veterinary medicinal products (IVMPs) classified as limited markets in line with Article 4(29) of Regulation (EU) 2019/6, but not eligible for authorisation under Article 23 of Regulation (EU) 2019/6.

1. Introduction

The importance of the availability of veterinary medicinal products is well recognised in the EU. Veterinary medicinal products legislation has been revised with the aim of reducing the administrative burden, enhancing the internal market and increasing the availability of veterinary medicinal products, while guaranteeing the highest level of public and animal health and environmental protection.

This led to the introduction of specific provisions for limited markets in Regulation (EU) 2019/6 of the European Parliament and the Council of 11 December 2018 on veterinary medicinal products repealing Directive 2001/82/EC (the Regulation). Article 4(29) of the Regulation provides a definition for limited market and Article 23 allows for the submission of a reduced package of safety and efficacy data when certain conditions are met.

Article 23 of the Regulation states that comprehensive safety or efficacy documentation, as defined in Annex II of the Regulation, shall not be required for limited markets applications, provided that the two conditions contained in that same provision are met.

Guidance on the safety and efficacy requirements for limited market products deemed eligible for consideration under Article 23 does exist (Guideline on data requirements for applications for immunological veterinary medicinal products intended for limited markets submitted under Article 23 of Regulation (EU) 2019/6 - 58 (EMA/CVMP/59531/2020)).

However, not all products that satisfy criteria to be classified as 'intended for a limited market' are automatically eligible for consideration under Article 23.[1].

Products meeting the 'limited market' definition in Article 4(29) of the Regulation but not meeting all conditions for limited markets application listed in Article 23 will require, by default, a comprehensive set of safety and efficacy documentation in accordance with the requirements in Annex II of the Regulation.

There is a practical need for specific scientific guidance describing how the general data requirements in Annex II can be adapted to products that meet the definition of limited market in Article 4(29) but

[1] The process for requests from applicants seeking either confirmation on classification of a product as intended for a limited market (as defined in Article 4(29) of Regulation 2019/6) and/or confirmation on eligibility for consideration in accordance with Article 23, is described in the 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).

are not eligible for authorisation under Article 23 of Regulation (EU) 2019/6, due to the characteristics of these products.

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

2. Scope

The purpose of this scientific guidance is to indicate how the flexibilities provided within Annex II can be applied with flexibility to immunological veterinary medicinal products that meet the definition of limited market under Article 4(29) of the Regulation are but not eligible for authorisation under Article 23 of the Regulation, due to the characteristics of these products. That is, while there is an obligation that the dossier complies with the requirements of Annex II, when scientifically justified, the flexibilities vis-à-vis data requirements available within Annex II can be applied for such products.

The safety and efficacy data requirements presented in this guideline are applicable to all applications for limited market immunological veterinary medicinal products as defined by Article 4(29), not eligible for authorisation under Article 23 of Regulation (EU) 2019/6.

3. Legal basis

This guideline should be read in conjunction with Regulation (EU) 2019/6, in particular Article 4(29), Article 8, Article 23 and Annex II.

If a product meets the definition of 'limited market' in Article 4(29) of the Regulation and the application is not eligible for authorisation under Article 23, then a comprehensive set of data will be required. The data requirements provided for in Annex II can accommodate some flexibilities because of the characteristics of the products concerned. This guidance aims to highlight where such general flexibility exists and how this flexibility may be applied to marketing authorisation applications for immunological veterinary medicinal products intended for limited markets but not eligible for authorisation under Article 23 of the Regulation, where scientifically justified.

Applicants should also refer to other relevant European and VICH guidelines.

In accordance with Annex II of Regulation (EU) 2019/6, all experiments on animals should be conducted taking into account the 3Rs principles (replacement, reduction and refinement) laid down in Directive 2010/63/EU on protection of animals used for scientific purposes.

4. Data requirements

Generally, the requirements as provided in section IIIb of Annex II to Regulation 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 also applicable to products for limited market products. The practical application thereof to specific dossiers will require a case-by-case assessment.

The safety and efficacy of the product under evaluation should be investigated and demonstrated in the target species. Interspecies extrapolation of pre-clinical or clinical data will be accepted whenever scientifically justifiable.

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 safety and efficacy data requirements of Annex II to Regulation 2019/6.

Scientific literature, reflecting current scientific knowledge may be used to support 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. The applicant should ensure that all relevant data, including data publicly available, are not subject to protection of technical documentation.

For IVMPs containing a GMO, the requirements stated in sections I.1.8 and IIIb.3E of Annex II of Regulation (EU) 2019/6 apply. 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 safety.

In Table 1, possible flexibilities concerning safety and efficacy data requirements as described in Annex II are highlighted and commented how this flexibility may be applied to marketing authorisation applications for immunological veterinary medicinal products intended for limited markets but not eligible for authorisation under Article 23 of Regulation (EU) 2019/6. The product information should reflect the data provided using standard statements, given in the QRD veterinary annotated product information template.

In addition, Annex II provides the following general considerations regarding flexibility for safety and efficacy requirements:

- Pre-clinical safety studies shall be carried out in compliance with good laboratory practice (GLP) requirements.

  Non-GLP studies may be accepted for non-target species studies as well as studies evaluating immunological, biological or genetic properties of the vaccine strains, under adequately controlled conditions. Other deviations shall be justified, and such studies might be considered acceptable if the design is appropriate to the stated objective of the study. Protocols and reports should allow a satisfactory assessment of the trial.

- Clinical trials (field trials) shall be conducted in compliance with established principles of good clinical practice (GCP). Deviations shall be justified. In case GCP is not applied, traceability, accuracy, integrity, and correctness of data should be ensured, and the use of such data in pivotal studies should be justified. Protocols and reports should allow a satisfactory assessment of the trial.

- Safety and efficacy studies shall be in line with the Ph. Eur. requirements. Deviations shall be justified.

- Appropriate parameters for the evaluation of efficacy should be established. 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 limited market product will be taken into consideration.
  In general, pre-clinical studies shall be supported by trials carried out in field conditions. When pre-clinical studies fully support the claims made in the summary of product characteristics, trials carried out in field conditions are not required.

5. 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/legal-content/EN/TXT/?uri=CELEX%3A02019R0006-20220128

2. Concept paper on scientific guidelines for limited market products deemed not eligible for authorisation under Article 23 of Regulation 2019/6 (EMA/CVMP/435071/2021)

   https://www.ema.europa.eu/en/scientific-guidelines-limited-market-products-deemed-not-eligible-authorisation-under-article-23

3. Guideline on data requirements for applications for immunological veterinary medicinal products intended for limited markets submitted under Article 23 of Regulation (EU) 2019/6 - (EMA/CVMP/59531/2020)

   https://www.ema.europa.eu/en/data-requirements-applications-immunological-veterinary-medicinal-products-intended-limited-markets

4. 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)

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.

Limited market product eligible for Article 23

Where the applicant provides evidence that a veterinary medicinal product is intended for a limited market **and** the benefit of the availability on the market of that product to the animal or public health outweighs the risk inherent in the fact that certain documentation has been provided (satisfies the conditions under Article 23(1)(a)(b) of Regulation (EU) 2019/6).

Limited market product as defined by Article 4(29), but not eligible for Article 23

Where the applicant provides evidence that a veterinary medicinal product is intended for a limited market **but** the benefit of the availability on the market of the veterinary medicinal product to the animal or public health does not outweigh the risk inherent in the fact that certain documentation has not been provided (does not satisfy the conditions under Article 23(1)(a) of Regulation (EU) 2019/6).

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.*

Table 1: Possible flexibility concerning safety and efficacy data requirements in Annex II for limited market IVMPs not eligible for Art. 23

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

No. of section	Section title	Data requirements	Applications for new Marketing Authorisations and relevant variations	
			Live	Others
3.A	General requirements	A **worst-case scenario** may be used for demonstration for safety for route and method of administration if scientifically justified.	✓	✓
		Data from larger combinations may be used, if justified.	✓	✓
		The use of pilot scale/R&D[2] batches that are representative for the manufacturing process described in the marketing authorisation application is possible.	✓	✓
		Safety studies for inactivated IVMPs may be combined with 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	✓
3.B	Pre-clinical studies (Laboratory safety studies)			
3.B.2	Safety of one administration of an overdose	Safety of an overdose, normally consisting of ten doses, shall be administered by each recommended route(s) and method(s) of administration to animals of the most sensitive categories of the target species, **unless the selection of the most sensitive of several similar routes is justified**.	✓	N/a
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 product information, unless a scientific justification for absence of risk is provided.	✓	✓

[2] Pilot batch: small scale industrial batch, representative of the production process described in the licensing dossier.
R&D batch: batch produced under laboratory conditions but representative of the production process described in the licensing dossier.

No. of section	Section title	Data requirements	Applications for new Marketing Authorisations and relevant variations	
			Live	Others
3.B.5	Examination of immunological functions	For inactivated vaccines, studies for the examination of immunological functions may be omitted. If necessary, relevant warnings should be given in the product information. For live vaccines where the pathogen is known to be immunosuppressive, a study should be conducted; based on the results of the study, relevant warnings should be given in the product information. If a live pathogen is not known to be immunosuppressive there is no need for study, and this must not be reflected in the product information.	✓	✓
3.C	Clinical trials (field studies)	Unless otherwise justified, results from pre-clinical studies shall be supplemented with data from clinical trials, using batches representative of the manufacturing process described in the marketing authorisation application. If pre-clinical studies adequately demonstrate the absence of a significant target animal safety risk, clinical studies are not required. It should be adequately justified that the data from the pre-clinical studies are representative for safety under field conditions. This includes the use of representative animals versus field conditions in the EU. Safety data from the field may still be required post authorisation. Both safety and efficacy may be investigated in the same clinical trials.	✓	✓
4.A	General requirements	Efficacy trials carried out in the laboratory shall be controlled trials, including untreated control animals unless this is not justified for animal welfare reasons and efficacy can be otherwise demonstrated.	✓	✓
		Data from larger combinations may be used, if justified.	✓	✓
		Efficacy studies for inactivated IVMPs may be combined with safety studies, and therefore, standard batches may be used with no requirements to demonstrate the efficacy with batches with batches formulated with minimum antigen content.	N/a	✓

No. of section	Section title	Data requirements	Applications for new Marketing Authorisations and relevant variations	
			Live	Others
4.B	Pre-clinical studies (Laboratory trials)	Unless otherwise justified, the onset and duration of immunity shall be established and supported by data from trials. Omission of studies such as duration of immunity is acceptable, provided that it is made clear in the product information that the data are not available.	✓	✓
		The influence of passively acquired maternally derived antibodies on the efficacy of vaccines when administered to animals at an age at which maternally acquired immunity is still present shall be adequately evaluated, if appropriate. Omission of studies such as effect of maternally derived antibodies (MDA), are acceptable, provided that it is made clear in the product information that the data are not available, and it should be scientifically justified.	✓	
4.C	Clinical trials (Field trials)	Unless otherwise justified, results from pre-clinical studies shall be supplemented with data from field trials, using batches representative of the manufacturing process described in the marketing authorisation application. Both safety and efficacy may be investigated in the same field trial.	✓	✓
		When pre-clinical studies fully support the claims made in the summary of product characteristics, trials carried out in field conditions are not required.	✓	✓
		Where pre-clinical studies cannot be supportive of efficacy, the performance of field trials alone may be acceptable.	✓	✓