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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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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 general aim of this guidance is to define acceptable data requirements for the demonstration of safety and efficacy of immunological veterinary medicinal products (IVMPs) classified as limited markets in line with Article 4(29) 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 the possibility to waive the submission 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.

Products meeting the 'limited market' definition in Article 4(29) of the Regulation but not meeting the 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) 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 general flexibilities provided within Annex II can be applied to limited market veterinary medicinal products as defined by Article 4(29) 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 general flexibility vis-à-vis data requirements can be applied for such products within the existing bounds of Annex II.

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 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 products intended for limited markets, where scientifically justified. Applicants should also refer to other relevant European and VICH guidelines listed in the references section.

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.

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 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, this guideline is only applicable for efficacy requirements. In accordance with the requirements of Directive 2001/18/EC, the full set of safety data as required in Annex II to Regulation 2019/6 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 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 products intended for limited markets. 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 general and, where applicable, specific 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.

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. Guideline on efficacy and target animal safety data requirements for applications for non immunological veterinary medicinal products intended for limited markets submitted under Article 23 of Regulation (EU) 2019/6 - (EMA/CVMP/52665/2020)

   https://www.ema.europa.eu/en/efficacy-target-animal-safety-data-requirements-applications-non-immunological-veterinary-medicinal

5. Guideline on safety and residue data requirements for applications for non-immunological veterinary medicinal products intended for limited markets submitted under Article 23 of Regulation (EU) 2019/6 - (EMA/CVMP/345237/2020)

https://www.ema.europa.eu/en/safety-residue-data-requirements-applications-non-immunological-veterinary-medicinal-products

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.*

The currently applied terminology for limited market product eligible for Article 23 and limited market product not eligible for Article 23 is as follows:

'Limited market product eligible for Article 23' – a product that meets the definition of limited market and, in addition, it is accepted that 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 (satisfies Article 23(1)(a) of Regulation (EU) 2019/6).

'Limited market product not eligible for Article 23' – a product that meets the definition of limited market, but it is not accepted that 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 (does not satisfy Article 23(1)(a) of Regulation (EU) 2019/6).

Table 1: Possible flexibility concerning safety and efficacy data requirements for IVMPs in Annex II

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/4.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.	✓	✓
		For live IVMPs **no passage requirement** in Annex II (except for reversion to virulence test). According to Ph. Eur. 5.2.6, a batch or batches of vaccine containing virus/bacteria at the least attenuated passage level that will be present in a batch of vaccine, should be used. The titre used in the studies should be adequately justified.	✓	N/a
		The use of pilot scale/R&D[1] 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.1	Safety of the administration of one dose	May be **part of the repeated dose study** required under point B.3 or **omitted if the results of the overdose study** required under point B.2 have revealed no major signs of systemic or local reactions.	✓	✓

[1] 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	Data requirements	Applications for new Marketing Authorisations and relevant variations	
			Live	Others
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**. Possible data reduction concerning used routes of administration.	✓	N/a
3.B.4	Examination of reproductive performance	Shall be considered when the IVMP is intended for use or may be used in pregnant animals or laying birds and when data suggest that the starting material from which the product is derived may be a potential risk factor. May form part of the safety studies described in points B.1, B.2, B.3 or of the clinical trials provided for the IVMP. If no studies performed, it needs to be clearly stated in the product information.	✓	✓
3.B.5	Examination of immunological functions	Where the IVMP might adversely affect the immune response of the vaccinated animal or of its progeny, suitable tests on immunological function shall be carried out. If it is usually unlikely for classical IVMP to affect the immune system, studies are normally not required. If necessary, relevant warnings should be given in the SPC.	✓	✓
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 as a post-authorisation commitment. Both safety and efficacy may be investigated in the same clinical trials.	✓	✓

No. of section	Section title	Data requirements	Applications for new Marketing Authorisations and relevant variations	
			Live	Others
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.	✓	✓
		For live IVMPs no passage requirement in Annex II. According to Ph. Eur. 5.2.7, the most attenuated passage level that will be present in a batch of vaccine should be used. The minimum titre should be adequately justified.	✓	N/a
		Unless otherwise justified, the onset and duration of immunity shall be established and supported by data from trials. If studies for duration of immunity are omitted, it must be made clear in the SPC 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. If such studies are omitted, it must be made clear in the SPC that the data are not available.	✓	✓
4.B	Pre-clinical studies (Laboratory trials)	For live vaccines, the product used for efficacy testing shall be taken from a batch or batches containing the minimum titre or potency. For other products, product from batches containing the minimum active content or potency expected at the end of the period of validity shall be used, unless otherwise 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.	✓	✓

No. of section	Section title	Data requirements	Applications for new Marketing Authorisations and relevant variations	
			Live	Others
		Where pre-clinical studies cannot be supportive of efficacy, the performance of field trials alone may be acceptable.	✓	✓

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