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

Draft

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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) entered into force on 28 January 2019 and is applicable from 28 January 2022 onwards. This regulation introduces specific provisions for applications for limited markets (Article 4 [29]).

Marketing authorisation applications for non-immunological veterinary medicinal products intended for limited markets, but not eligible for authorisation under Article 23 of Regulation (EU) 2019/6 should contain comprehensive information on safety as provided for under Annex II of Regulation (EU) 2019/6. However, having regard to the specificities of veterinary medicinal products intended for limited markets (i.e. the fact that they are intended for diseases that occur infrequently or in limited geographical areas, or for species other than cattle, sheep for meat production, pigs, chickens, dogs and cats), and with the aim of promoting availability for such diseases or species, certain adaptations within Annex II may be acceptable, provided that the data submitted in the dossier are sufficient to demonstrate the safety of the veterinary medicinal product. It is the intention of the guideline to highlight flexibility within Annex II and also with regard to other guidance on the data requirements for safety and residues for this type of application. However, it is recognised that this is not always feasible as not all scenarios can be addressed in a general guidance document.

1. Introduction (background)

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 of 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.

Products meeting the 'limited market' definition in Article 4(29) of the Regulation but not meeting the conditions for limited markets applications 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.

Article 8(1)(b) of the Regulation requires applicants to provide the technical information that is necessary to demonstrate the quality, safety and efficacy of the veterinary medicinal product. However, due to the specificities of veterinary medicinal products intended for limited markets (i.e. the fact that they are intended for diseases that occur infrequently or in limited geographical areas, or for species other than cattle, sheep for meat production, pigs, chickens, dogs and cats), and with the aim of promoting availability for such diseases or species there is a practical need for specific scientific guidance describing how the general data requirements on safety in Annex II can be adapted to products that meet the definition of limited market in Article 4(29).

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 specificities of veterinary medicinal products intended for limited markets (i.e. the fact that they are intended for diseases that occur infrequently or in limited geographical areas, or for species other than cattle, sheep for meat production, pigs, chickens, dogs and cats), and with the aim of promoting availability for such diseases or species. 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.

For authorisation of any veterinary medicinal product, it is expected, as a basic principle, that the safety of the product for the user, the environment and the consumer (in the case of products intended for food producing animals) will be assured. This may be achieved by the provision of relevant data to conclude on the safety and, if needed, by applying appropriate measures to mitigate any risks identified. In the absence of data, potential risks cannot be excluded and, therefore, relevant risk mitigation measures should be proposed. This principle also applies to limited market products.

As safety must always be assured, default waivers from standard Annex II requirements cannot be identified. However, whilst Annex II provides the high-level requirements, the detailed approaches and study designs for addressing these requirements are typically described in CVMP and VICH guidelines. Some flexibility always exists in relation to guidelines, with the possibility for applicants to provide scientific justification for deviating from these guidelines. In light of the background to this guideline provided in the Introduction, the CVMP will take particular care to give full consideration to arguments for deviating from safety guideline recommendations and, wherever possible, to look upon these in the most favourable light.

3. Legal basis

This guideline should be read in conjunction with Regulation (EU) 2019/6, in particular Article 8(1)(b), Article 23 and Annex II.

Applicants should also refer to other relevant European and VICH guidelines listed in the references section.

4. Applications for authorisations for veterinary medicinal products other than biologicals (pharmaceuticals)

4.1. Safety data requirements

The requirements for Marketing Authorisations for pharmaceuticals are detailed in Annex II of Regulation (EU) 2019/6 where some flexibility is already envisaged. Any omission of safety data shall be scientifically justified.

In lieu of safety studies, literature data including European public MRL assessment reports (EPMARs) or MRL summary reports may be used, provided that the data they contain are not subject to protection

of technical documentation having regard to Articles 38 to 40 of Regulation (EU) 2019/6 or that permission to access those data is granted by the data owner. These data can also be used for marketing authorisation applications intended for non-food producing species, if available. General requirements for published studies are outlined in Annex II of Regulation (EU) 2019/6.

It is recognised that existing literature studies may not always satisfy current GLP or guideline standards and that published documentation may not be detailed enough to undertake an independent assessment. Inclusion of bibliographic data will need, therefore, a thorough evaluation as to the reliability and relevance of this information.

Summaries of studies for which detailed reports are not available shall not be accepted as valid documentation.

The above principles apply the same way to limited market applications under article 8 and to non-limited market applications under article 8.

4.1.1. Pharmacological data

Pharmacological studies conducted in experimental animals and target species, or reliable bibliographic data (see section 4.1) adequately describing the mechanism of action and the fate of the active substance and its metabolites shall be included. Cross reference may be made, if applicable, to studies submitted in Part 4 of the dossier. This applies the same way to limited market applications under article 8 and to non-limited market applications under article 8.

4.1.2. Toxicological data

When there is no MRL Summary Report or EPMAR/bibliographic data available, toxicological studies are required for the evaluation of user safety and the assessment of adverse effects in the target species. Even when an MRL Summary Report or EPMAR is available additional data might be needed in rare cases due to the route of exposure.

Potential exposure of the user associated with administration, such as exposure by inhalation, dermal contact or accidental self-injection should be considered. The omission of studies should be adequately justified.

Regarding repeat-dose toxicity, a study in one species of laboratory animal shall normally be sufficient. This study may be replaced by a study conducted in the target animal, if all relevant information to perform the User Risk Assessment is available from this study. CVMP/VICH guidelines should be followed and the toxicological tests themselves should be conducted in accordance with the relevant OECD guidelines or other internationally recognised guidelines and any deviation should be justified. This applies to limited market applications under article 8 and to non-limited market applications under article 8 but deviations from guidelines may be more easily accepted for limited market applications. No general recommendation can be given in this regard. Deviations will be assessed on case-by-case basis.

4.1.3. User safety assessment

For authorisation of any veterinary medicinal product, the safety of the product for the user shall be assured. A user risk assessment, including risk management proposals if needed, must be submitted for all limited market applications.

Information from safety data should be used for risk assessment. Generally, the principles of the user safety guideline (EMEA/CVMP/543/03-Rev.1) and/or the guideline on user safety of topically administered products (EMA/CVMP/SWP/721059/2014) should be applied. The assessment should include a discussion of the effects found in the pharmacological and toxicological data and relate these to the type and extent of human exposure (i.e. acute or chronic) to the final veterinary medicinal product with a view to formulating appropriate user warnings.

As indicated in EMEA/CVMP/543/03-Rev.1, it is noted that for some endpoints standardised methods are currently not available, in particular for parenteral toxicity and respiratory sensitisation. However, for parenteral toxicity, target animal safety studies may provide adequate information on local and systemic effects following this route of exposure. Data on skin sensitisation may serve as a surrogate for respiratory sensitisation, in the absence of appropriate methods.

For toxicity studies on local effects, the formulation of the product should be preferably used. However, in the interest of reduced testing in animals, if there are only historical data or published literature on the ingredients in the formulation, the potential effects of a product can be deduced from these data.

The need for any additional studies depends on the exposure and any identified gaps in data and in some cases, the nature of the substances indicates the need to focus on specific endpoints of toxicity or pharmacology.

Whenever possible, available information on the severity of an effect at the anticipated exposure levels should be taken into account as well. If such information is not available, it must be assumed that the effects will occur at any exposure level.

To account for uncertainty in extrapolating animal data to humans (inter-species variability), the variation in sensitivity among humans (inter-individual variability), quality of data, severity of response, differences in exposure (route, duration, frequency) compared to that applied in the study from which the toxicological reference values were derived, or other concerns; a numerical factor applied to a toxicological (pharmacological /microbiological) endpoint can be applied. These factors may be default values used in the absence of specific information on a substance and may be modified in the light of specific information. When alternative factors are proposed, consideration must be given to the guidance document published by the IPCS/WHO (IPCS/WHO, 2005).

When there is a predicted risk for the user, appropriate measures for risk reduction should be proposed and evaluated.

The above principles apply to limited market applications under article 8 and to non-limited market applications under article 8.

4.1.4. Environmental safety

4.1.4.1. For food producing species

In line with VICH GL 6, the assessment stops at Question 4, and further new Environmental Risk Assessment (ERA) is not required for a Limited Market application providing that the following conditions are met:

a. An ERA is available for a product containing the concerned active substance/s, and this ERA has been carried out in line with VICH GL 6 and GL 38, and the CVMP/VICH GL in support of GL 6 and 38 (EMEA/CVMP/ERA/418282/2005). The existing ERA must have been previously assessed and accepted in a member state, or by the CVMP.

b. The available ERA belongs to the same applicant or access rights should have been granted. All data have to be made available in the Limited Market application.

c. The target species of the Limited Market application is reared in similar conditions as the target species of the available ERA and the primary release is to the same environmental compartment as the available ERA, i.e. soil, water, dung.

d. The environmental exposure and the total administered dose of the Limited Market application is not higher than the one in the available ERA. Species-based exposure refinements (e.g. based on metabolism or on degradation in manure) can only be extrapolated to the Limited Market species of concern if the applicant is able to scientifically substantiate the similarities between the rearing and metabolism between both species. If this cannot be done, the refinements used in the existing ERA cannot be considered.

e. Any risks identified in the available ERA have to be considered for the Limited Market application. This includes environmental information included in product literature, such as risk mitigation measures and disposal advice present.

If any of these requirements are not fulfilled, the limited market application should be accompanied by an ERA carried out in compliance with the current guidance.

The above applies the same way for limited market applications under article 8 and under article 23.

4.1.4.2. For non-food producing species

In accordance with VICH GL6 and the Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38 (EMA/CVMP/ERA/418282/2005-Rev.1- Corr), the assessment stops at question 3 and no further assessment will be required, in principle, for non-food producing animals.

This applies to all applications.

4.2. Residue data requirements

Food derived from other species than cattle, sheep for meat production, pigs and chickens usually constitutes a small proportion of the diet of the average European consumer. It may nevertheless, constitute a significant portion of the intake of animal derived products in certain geographic areas or certain subpopulations and, therefore, consumer safety must be guaranteed.

The requirements for marketing authorisations for pharmaceuticals are detailed in Annex II of Regulation (EU) 2019/6, where some flexibility is already envisaged. Any omission of residue data or the inclusion of an alternative approach to setting withdrawal periods shall be indicated and discussed. Residue depletion studies aim to permit the determination of withdrawal periods necessary to ensure that no residues, which may constitute a hazard for consumers, are present in foodstuffs obtained from treated animals.

The withdrawal period refers to, and is dependent on, the specific formulation, species, route of administration and dosing regimen (relevant are the highest dose and longest duration indicated for a particular species) of a veterinary medicinal product (VMP).

Guidelines with specific requirements on setting withdrawal periods on limited market species as fish (VICH GL57) and bees (VICH GL56) should be followed. Other guidelines on setting withdrawal periods do not differentiate between limited or non-limited market species.

Studies in mammals and birds shall be performed according to VICH GL48 and other relevant guidelines since this will lead to the optimum (i.e. shortest safe) withdrawal period. However, having regard to these limited market products and with the aim of promoting availability, certain adaptations within Annex II may be acceptable, provided that the data submitted in the dossier are sufficient to demonstrate the consumer safety of the veterinary medicinal product.

Therefore, if residue data entirely in accordance with these guidelines are available for a related specie(s) for the VMP concerned and all the following conditions are met:

- the pharmacokinetic of the VMP is comparable between species,
- the active substance contained in the VMP has the same MRL in both (limited and non-limited market) species, or a lower MRL in the non-limited market species,
- the route of administration is identical,
- the dose and volume of injection, if applicable, are no greater than those administered in the non-limited market species,

residue depletion studies might not be necessary and the extrapolation of withdrawal periods from the related species might be accepted. In this case a justified additional minimum safety factor 1.5) should be used to compensate for possible species differences (e.g. cattle to goats).

If the abovementioned conditions are met, a reduced residue depletion study to confirm the withdrawal period of the related species could be also accepted, provided that any deviation from the guideline approach (e.g., reduction in the number of slaughter times or reduced data in selected withdrawal period determining tissue(s)) is scientifically justified and supported by adequate data. A safety factor might be necessary.

Additional residue data are always needed for products having a potential to leave local residues (in particular injectable products administered intramuscularly and/or subcutaneously as well as dermal/intramammary applications, as described in relevant bioequivalence guideline EMA/CVMP/016/2000). However, a reduced residue depletion study to confirm the withdrawal period could be accepted if scientifically justified. A safety factor might be necessary.

The above principles of extrapolation apply to limited market applications under article 8.

For compounds for which it was not necessary to establish numerical MRLs (substances which are classified as 'No MRL required' in Table 1 of the Annex to Commission Regulation (EU) No 37/2010), the Guideline on determination of withdrawal periods for edible tissues (EMA/CVMP/SWP/735325/2012 Rev.2*) provides the recommendations to select other reference values that may be used.

For the residue depletion study (studies) with the VMP concerned, the analytical method shall be performed in accordance with VICH GL 49. The analytical method shall have regard to the state of scientific and technical knowledge at the time the application is submitted. This applies to all applications.

In any case, provisions concerning protection of technical documentation (especially according to Articles 38 to 40 of Regulation (EU) 2019/6) are applicable. Reference to pharmacokinetic and residue data of EPMARs (e.g. data underlying the withdrawal period) can only be made if the data used are not protected or if applicants have otherwise legal access to the data. This applies to all applications.

5. Applications for authorisations for biological veterinary medicinal products other than immunologicals

Biological veterinary medicinal products other than immunological veterinary medicinal products contain an active biological substance, which is produced by or extracted from a biological source and that needs for its characterisation and for the determination of its quality a combination of physico-chemical-biological testing, together with knowledge of the production process and its control. The data requirements for Marketing Authorisations as given in the Annex II of Regulation (EU) 2019/6 and the CVMP/(V)ICH Safety guidelines were considered. Generally, the data requirements for safety testing (i.e., pharmacology and toxicology) are identical to the requirements for pharmaceuticals (see respective chapters). However, flexibility in the data requirements is already allowed for all biologicals, independently of their limited market status. Furthermore, the flexibility envisaged for pharmaceutical products intended for limited markets is also applicable to biological products intended for limited markets.

Also, for establishment of withdrawal periods for biological 'limited market' VMPs, the same principles as laid down for pharmaceuticals 'limited market' can be applied.

Definitions

For the purpose of the present guideline, the following definitions apply:

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 not been provided (satisfies the conditions under Article 23(1)(a) 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).

Biological veterinary medicinal product

According to Article 4 (6) of Regulation (EU) 2019/6 of 11 December 2018 'Biological veterinary medicinal product' means a veterinary medicinal product where an active substance is a biological substance.

Biological substance is defined as 'a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of

physico-chemical-biological testing, together with knowledge of the production process and its control' (Article 4(7)).

Immunological veterinary medicinal products

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.

Withdrawal period

According to Article 4 (34) of Regulation (EU) 2019/6 'withdrawal period' means the minimum period between the last administration of a veterinary medicinal product to an animal and the production of foodstuffs from that animal which under normal conditions of use is necessary to ensure that such foodstuffs do not contain residues in quantities harmful to public health.

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. 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
3. 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/documents/scientific-guideline/concept-paper-scientific-guidelines-limited-market-products-deemed-not-eligible-authorisation-under/6_en.pdf
4. 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)
5. 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)
6. 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)
7. Guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-Rev.1)
8. Guideline on user safety of topically administered veterinary medicinal products (EMEA/CVMP/SWP/721059/2014)
9. VICH GL48: Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: marker residue depletion studies to establish product withdrawal periods

10. VICH GL56: Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: study design recommendations for residue studies in honey for establishing MRLs and withdrawal periods (EMA/CVMP/VICH/176637/2014)
11. VICH GL57: Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing species: marker residue depletion studies to establish product withdrawal periods in aquatic species (Draft: EMA/CVMP/VICH/517152/2013)
12. VICH GL49: Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: validation of analytical methods used in residue depletion studies (EMA/CVMP/VICH/463202/2009)