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

Draft

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Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Guideline on safety and residue data requirements for applications for non-immunological veterinary medicinal products intended for limited markets submitted under Article 23 of the 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 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 regarding safety and residues for marketing authorisation applications for non-immunological veterinary medicinal products intended for limited markets submitted under Article 23 of Regulation 2019/6.

It is the intention of the guideline to indicate options to reduce data requirements for this type of application; however, it is recognised that a reduction in critical data needed for adequate characterisation of safety may not always be feasible as different scenarios require different data and not all scenarios can be anticipated in a general guidance document. 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 animals) will be assured. This may be achieved either by the provision of relevant data and/or by applying appropriate measures to mitigate risks identified or potential risks that cannot be excluded due to absence of data. Data requirements to identify potential toxicity in the target species depend on the evaluation of the benefit-risk balance of the particular product and, therefore, additional scope for reductions may exist and comprehensive safety assurance may not be required for the target animal in each case (see also Guideline on efficacy and target animal safety data requirements for non-immunological veterinary medicinal products intended for limited markets applications submitted under Article 23 of the Regulation (EU) 2019/6).

1. Introduction

From 2006 to 2017, the CVMP developed guidelines on data requirements for MUMS/limited market veterinary medicinal products for quality, safety and efficacy for pharmaceuticals with the aim to stimulate research, development and innovation of new veterinary medicines intended for minor uses and minor species (MUMS/limited markets). 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 limited markets including definition of limited market and specific conditions for granting derogation to the data requirements defined in Annex II of the Regulation. The current limited markets guideline has been drafted in line with the new legal provisions, including consideration of data requirements for biological veterinary medicinal products other than immunological veterinary medicinal products.

It is the intention of the guideline to provide clear guidance on the circumstances under which data requirements can be reduced for limited market product applications submitted in accordance with Article 23 of Regulation (EU) 2019/6, to facilitate the applicant's work for estimating the required resources for such applications, preparing the application dossier and providing predictability of the assessment.

However, the guidance provided in this document is general and it is recognised that not all scenarios can be addressed. If in doubt about the precise requirements for specific applications, applicants are recommended to request scientific advice to confirm the appropriateness of a proposed data package.

2. Scope

The objective of this guideline is to clarify the data requirements for marketing authorisation applications for limited markets submitted under Article 23 of Regulation 2019/6:

- for veterinary medicinal products other than biologicals, and
- for biological veterinary medicinal products other than immunologicals.

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

The current guideline addresses requirements for consumer safety, user safety, environmental safety and data to identify potential toxicity of the veterinary medicinal product in target species. Specific preclinical and clinical requirements relating to target animal safety are addressed in a separate guideline (Guideline on efficacy and target animal safety data requirements for non-immunological veterinary medicinal products intended for limited markets applications submitted under Article 23 of the Regulation (EU) 2019/6).

As a general principle, the CVMP and VICH guidelines concerning safety and residues are applicable to limited market products.

In accordance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes and Directive 2010/63/EU on protection of animals used for scientific purposes, the 3R principles (replacement, reduction and refinement) should be applied to all testing involving animals.

3. Definitions

Limited market

According to Article 4 (29) of Regulation (EU) 2019/6 of 11 December 2018, '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.

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)).

Veterinary medicinal products other than biologicals

This group contains all veterinary medicinal product where the active substance is not a biological substance. For reasons of simplification for the scope of this guideline, these products are named "Pharmaceuticals".

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.

Related Species

In terms of this guideline, withdrawal periods may be extrapolated between 'related species' and food commodities (as defined in Commission Regulation (EU) 2017/880) under the conditions described in section 5.1.2.2.

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, Title I for veterinary medicinal products other than biological veterinary medicinal products and Title IIa for biological veterinary medicinal products other than immunological veterinary medicinal products.

One of the main objectives of Regulation (EU) 2019/6 is to promote availability of veterinary medicinal products and as laid down in the preamble of Regulation (EU) 2019/6, recital 30 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 Title III (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 can demonstrate 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. Applications for authorisations for veterinary medicinal products other than biologicals (pharmaceuticals)

5.1. Safety data requirements

The requirements for Marketing Authorisations for pharmaceuticals are detailed in Annex II of Regulation (EU) 2019/6. The documentation accompanying the limited market application shall be presented in accordance with the general requirements and deviations from the data requirements shall be scientifically justified. Generally, the submitted data package for limited market applications shall be appropriate for the evaluation of safe use of the veterinary medicinal product. That is, for authorisation of any veterinary medicinal product, it is expected, as a basic principle, that, the safety of the product for the user, the consumer (in the case of products intended for food animals) and the environment will be assured. This may be achieved either by the provision of relevant data and/or by applying appropriate measures to mitigate risks identified or potential risks that cannot be excluded due to absence of data. Data requirements to identify potential toxicity in the target species depend on the evaluation of the benefit-risk balance of the particular product and, therefore, additional scope for reductions may exist and comprehensive safety assurance may not be required for the target animal in each case (see also Guideline on efficacy and target animal safety data requirements for non-immunological veterinary medicinal products intended for limited markets applications submitted under Article 23 of the Regulation (EU) 2019/6). For limited markets, no general recommendation for omission of specific documentation or data reduction can be given, but it is in principle possible to waive or vary standard requirements on a case-by case basis. The minimum acceptable documentation is dependent upon the individual substance/product, conditions of use and the relevant exposure scenarios and should be scientifically justified.

When considering data waiving, it should be kept in mind that pharmacological and toxicological documentation are used to provide hazard identification for both the animal and the user. Hence, studies or other appropriate documentation regarding a certain endpoint might be needed to address one of these aspects but not necessarily the other. For example, a user risk might be low because repeated exposure (e.g. by self-injection) is unlikely while repeated dosing in target animal might trigger the need for a repeated-dose toxicity study (further data requirement for efficacy and TAS for

limited markets can be found in the Guideline on efficacy and target animal safety data requirements for non-immunological veterinary medicinal products intended for limited markets). For limited market applications, data requirements might also be waived when reasonable risk mitigating measures can be implemented for users (see also chapter 6.1.1.1.).

Bibliographic data including European public MRL assessment reports (EPMARs) may be used, provided that the data they contain are not subject to protection of technical documentation (especially according to Articles 38 to 40 of Regulation (EU) 2019/6) or that permission to access those data is granted by the data-owner. General requirements for bibliographic data are outlined in Annex II of Regulation (EU) 2019/6. These also apply to limited market applications. 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, therefore, need a thorough evaluation as to the reliability and relevance of this information. An example of a commonly recommended method for study evaluation is the one proposed by Klimisch et al. in 1997.

Complementarily or alternatively to standard requirements and data reduction options above, for the purpose of supporting "limited markets", it is possible to use endpoint specific surrogate (non-Annex II/non-guideline) approaches, if adequately justified. While most surrogate methods may have limitations, especially as to their use as standalone methods for quantitative (endpoint-related) hazard assessments, they may nevertheless prove appropriate and useful to screen and identify particular hazards, to inform the hazard assessment and to determine if specific mitigation measures are warranted. Examples of these surrogate approaches include ex-vivo/in-vitro approaches or in-silico tools including (quantitative) structure-activity relationships ((Q)SAR), extrapolation of existing data (e.g. short term to long term toxicity), prediction of endpoint information for one substance by using data for the same endpoint from (an)other substance(s) ("read-across" techniques), thresholds of toxicological concern (TTC) or Cramer Class scheme in conjunction with the associated TTC values.

Any of the surrogate approaches or combination of approaches should be scientifically justified and valid, and adequately reported. Adequacy, reliability and limitations as well as the experimental/methodological conditions used should be thoroughly discussed and assessed. Care should be taken to identify limitations and uncertainties and to assess their impact on the estimate of the respective hazard/risk and the benefit-risk balance.

Where studies are considered necessary, applicants are encouraged to use, whenever possible, validated in vitro protocols (i.e. VICH, OECD) to replace laboratory animal studies. However, should standard animal studies be necessary, they should follow relevant scientific protocols (VICH, OECD). Since in accordance with Directive 2010/63/EU duplicative tests and studies on vertebrates should be avoided, marketing authorisation holders are encouraged to share results of studies and costs of these studies on reasonable terms with applicants of limited market products.

When the active substance is novel in veterinary medicine with only limited prior information and regulatory experience available or when there is special concern, there may be less scope for data reductions and a more comprehensive safety data package may be required.

In accordance with Annex II, Title III, 8, further data to evaluate safety for the animal or the user in addition to the general data requirements as laid out in Annex II might be necessary for novel therapy marketing authorisations.

Should the conducted studies and the submitted data not be sufficient and in the absence of appropriate scientific justification, standard toxicity studies might be necessary. Therefore, it is strongly recommended to seek scientific advice before submission of the application. This applies

particularly to the use of surrogate approaches, as this is an area where methodologies and knowledge are evolving fast, but still limited experience and guidance exists regarding their regulatory use.

5.1.1. User safety assessment

For authorisation of any veterinary medicinal product, including those deemed eligible for submission under Article 23, it is expected, as a basic principle, that, the safety of the product for the user will be assured. This may be achieved either by the provision of relevant hazard and effect data and/or by applying appropriate measures to mitigate risks identified or potential risks that cannot be excluded due to absence of data. A user risk assessment, considering the administration of the product and other potential routes of accidental exposure, and risk management proposals must be submitted for all limited market applications. Information from safety data should be used for hazard assessment. For the calculation of human exposure, realistic theoretical considerations can be used, and study data can in most cases be substituted by theoretical models. The principles of the user safety guideline (EMEA/CVMP/543/03-Rev.1) and 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. For limited market products, a worst-case assumption can be made when toxicological studies are omitted in some cases. In these instances, sufficiently protective and reasonable risk mitigating measures should be put in place. For example, an "unknown" risk for developmental effects might in some cases be mitigated for the professional user by warnings for pregnant women or women trying to conceive to avoid handling the product. However, an "unknown" risk of genotoxicity might be acceptable for single/ infrequent uses in a target animal (given a relevant countervailing benefit of the veterinary medicinal product) but it is most probably not acceptable for the user, when there is a certain likelihood of exposure, especially for non-professionals. In this case the product might need severe restrictions for user safety reasons or could not be placed of the market because a major potential risk cannot be mitigated. In case reasonable risk mitigating measures are not possible, unlikely to be adhered to by users or there is a special concern, a toxicological study or other sufficient information to characterize the hazard shall be provided. Limited information or surrogate method-based information might lead to additional uncertainty which will be factored into the respective hazard estimates, where necessary.

5.1.2. Environmental safety

5.1.2.1. For food producing species

For product applications submitted under Article 23, a reduction in data requirements relative to what is provided for in VICH GL 6 is not foreseen. In line with VICH GL 6, Question 4, an Environmental Risk Assessment (ERA) is not required for a Limited Market application for terrestrial species, 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 is not applicable to applications for Limited Market for species reared in aquaculture as, according to the definition of limited market species in Regulation 2019/06, there are no aquatic major species to refer to.

In case an applicant for a Limited Market application wishes to deviate from the studies requested in the VICH GL 38, the applicant is encouraged to ask for Scientific Advice.

5.1.2.2. For non-food producing species

Environmental safety requirements should be addressed by referring to the VICH GL 6 (CVMP/VICH/592/98-FINAL).

5.2. Residue data requirements and withdrawal periods

The withdrawal period refers to, and is dependent on, the specific formulation and dosing regimen (relevant are the highest dose and longest duration indicated for a particular species) of a veterinary medicinal product (VMP) [1].

Each product has to be considered on its own merits.

The following approach applies to procedures for VMPs for indications and/or species that fit the definition provided in Article 4 (29) of Regulation (EU) 2019/6 ('limited market') when the application is submitted under article 23 of this Regulation.

5.2.1. Points to consider

In the process of collecting data with the aim to establish withdrawal periods for 'limited market' VMPs several factors and questions may need to be taken into account:

- Is there a veterinary medicinal product containing the same qualitative and quantitative concentrations/amounts of active substance(s) and excipients already authorised for another indication in the same species or for another food-producing species?

[1] Please note that this is different in MRL assessment, which refers to the active chemical substance itself.

- Is there another veterinary medicinal product already on the market which has certain differences in formulation or conditions of use compared to the 'limited market' product: are the differences considered relevant in terms of pharmacokinetics and residue depletion or not?
- Is the intended dose lower, identical or higher compared to the dose the VMP is already authorised for (for products already authorised in a major market)?
- Is the active substance well known for use in the concerned food producing species or other (preferably related) food-producing species in terms of pharmacokinetics and residue depletion, i.e. is there regulatory experience with similar products (e.g., the extent to which the substance has been used)? Is there detailed bibliography on the substance/product available?
- Does the VMP in its formulation have the potential to leave local residues like e.g. products for intramuscular or subcutaneous use or products for topical use? Or is the product intended for intravenous or oral use and does not have the potential to leave local residues?
- Does the active substance possess accumulating properties (e.g. Log P_{ow} > 3) or otherwise relevant tissue binding/persistence properties in certain edible tissues (like e.g. gentamicin)?
- Is the VMP a long-acting or sustained-release (bolus) formulation?
- Does the active substance contained in the VMP have lower, identical or higher MRLs for the species related to limited markets compared to the species the product is already authorized for?
- The active substance(s) and excipients used should be covered by regular MRL procedures according to Commission Regulation (EU) No. 470/2009 or considered as not falling within the scope of this regulation ("out-of-scope") or included in the list of biological substances considered as not requiring an MRL evaluation.

The above factors and questions are examples only and are intended to illustrate critical points to consider when identifying data requirements and assessment options for withdrawal periods for VMPs for limited markets. Additional points could also be relevant depending on the properties and use of the intended product.

In any case, provisions concerning protection of technical documentation (especially according to Articles 38 to 40 of Regulation (EU) 2019/6) are applicable for VMPs for 'limited markets'. Reference to pharmacokinetic and residue data of other products (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 (e.g. the MAH is identical to the one owning the authorisation for the reference VMP). This also applies to any procedures involving extrapolation of withdrawal periods.

5.2.2. General considerations on the approach to obtain a withdrawal period

Given that there is a wide variety of pharmacologically active substances, formulations and conditions of use of VMP and possible scenarios encountered, this guidance is necessarily general and does not deal with detailed case-specific recommendations. The considerations below are intended to guide applicants to choose appropriate options and strategies for obtaining a product-tailored withdrawal period for a 'limited market' product.

The optimum (i.e. shortest safe) withdrawal period can be obtained using an approach according to Annex II of Commission Regulation (EU) 2019/6 and the relevant CVMP/VICH GLs; i.e. VICH GL48 for edible tissues including meat, milk and eggs, VICH GL57 for aquatic species, and VICH GL 56 for

honey. The VICH GLs are considered the "gold standard" for generating suitable data to assess withdrawal periods.

For VMPs fulfilling the criteria for limited markets it is, however, possible to deviate from the guideline approach under certain conditions and product-specific documentation can be reduced or even omitted, and alternative methodology may be used.

The approaches or combinations of approaches described below can be used (Options i and ii).

The degree of additional uncertainty that may be introduced (compared to the standard approach in line with VICH GLs) will be assessed case-by-case and may be reflected in substantially extended withdrawal periods.
Applicants are strongly encouraged to seek scientific advice when considering use of reduced documentation and alternative study designs or strategies to support a withdrawal period.

If the use of alternative non-guideline approaches is not possible, applicants are required to submit data in line with to Annex II and relevant VICH GLs.

Option i.) For VMPs, where reference can be made to another product containing the particular active substance, withdrawal periods can be extrapolated under certain conditions:

Identical withdrawal periods can be applied if a VMP containing the same qualitative and quantitative concentrations/amounts of active substance(s) and excipients is already on the market for the same target species, and the application within the scope of 'limited markets' concerns a new/additional indication and the dosage regimen remains the same. In case reference is made to another product, the applicant needs to ensure that the VMP authorised for a non-limited market species has a full Annex II-compliant dossier and that protection of technical documentation (especially according to Articles 38 to 40 of Regulation (EU) 2019/6) does not apply.

In order to extrapolate the withdrawal periods between products in the same species, bioequivalence or other comparative pharmacokinetics according to the 'Guideline on the conduct of bioequivalence studies for veterinary medicinal products' (EMA/CVMP/016/2000-Rev.3-corr.) needs to be shown for the VMPs or justification as to why such studies can be waived needs to be provided.

The extrapolation of withdrawal periods via the "bioequivalence" approach may analogously also be applied for related species[2] according to Article 4 (29b) of Regulation (EU) 2019/6. In this case a justified additional precautionary safety factor (minimum factor 1.5) should be used to compensate for possible species differences (e.g. cattle to goats) that may not become evident in the bioequivalence test.

Additional residue data are 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 guidelines). This data could be generated using, where appropriate, a limited residue depletion study (e.g., at 2 time points, one just before the reference withdrawal period and one after it, also using the approach of multiple injection sites per animals as described in VICH GL 48, or an approach in line with Option ii, below) - use of this approach would only be appropriate if the dose and volume of injection for the new VMP are not higher than that administered for the VMP authorised for use in species not related to 'limited markets' and MRLs are identical or higher for the species related to 'limited markets'.

[2] As defined in CR (EU) 2017/880.

If the dosage[3] intended to be applied for the 'limited market' VMP is higher than the one for the product already on the market, if the excipients have the potential to significantly alter residue depletion, if the VMP contains a long-acting formulation and/or if MRLs for the "limited market" species are lower, residue depletion data in line with VICH GLs are needed. Alternatively, applicants may decide to use approaches for VMPs where no reference to an existing withdrawal period can be made, which is described in Option ii.

Where residue studies with the VMP concerned are conducted, the analytical method must be validated in line with VICH GL 49 (EMA/CVMP/VICH/463202/2009) or according to equivalent criteria.

Option ii.) If no reference to the withdrawal period is made, the alternative Option ii can be pursued

As described above, applicants can choose to generate data according to VICH GLs or extrapolate withdrawal periods from a VMP authorised for a non-limited market species if possible. If applicants wish to establish a withdrawal period more tailored to the individual product, based on reduced data sets or alternative approaches (i.e. no full VICH GL compliant study) it is possible under certain conditions.

Any such proposal needs to be thoroughly justified and supported by appropriate scientific evidence, particular attention should be paid to any missing information, and sound justification should be given as to why demonstration of an appropriate withdrawal period can be supported although certain information is lacking.

Different strategies and combinations of data of different types/sources and tools may be useful and applicable. The examples below are informational only and not intended to limit the range of methodological options and data sources.

- Based on adequate scientific justification, a limited residue depletion study based on a design described in VICH GL48 can be used to substantiate a withdrawal period, e.g. a single/limited time point study design (e.g., at 1 suitably selected time point in analogy to the design for a "zero" withdrawal period in VICH GL 48 or at 2 time points, one just before the anticipated withdrawal period) or, for substance leaving local residues, the use of a concept of multiple injection sites per animal (e.g., for intramuscular or subcutaneous use) could allow to generate suitable data on local residues at injection sites. It may also be possible to provide, based on adequate scientific justification, reduced data in selected withdrawal period determining tissue(s) only (e.g., tissue with highest residues and the slowest depletion rate).

- Suitable information could also be derived from available data generated in line with VICH GL 46 (e.g. supporting ADME data) or by using metabolism data generated in line with VICH GL 47.

- Appropriate data may also be obtained from bibliographic information (including EPMARs, provided that protection of technical documentation according to Articles 38 to 40 of Regulation (EU) 2019/6 does not apply) on the substance and other similar products. This includes bibliographic approaches using "read across" techniques, i.e. use of appropriate data in related species and for structurally similar substances or for comparable formulations/products. Use of bibliographic data will need a thorough evaluation as to their reliability and relevance, preferably using a commonly recognised method (an example may be Klimisch et al.,1997 or equivalent). Published studies should contain a sufficient amount of data and details to allow an independent assessment. Analytical methods used should be validated, preferably in line with VICH GL 49 (EMA/CVMP/VICH/463202/2009) or guidelines using comparable criteria.

[3] Refers to total dose (total amount of drug administered) considering the dosing regimen for the drug.

- Where other suitable data and validated in-silico models are available, these may be used to support proposals for a withdrawal period.

5.2.3. Honey

The approaches based on reduced data are not applicable for VMPs for use in honey bees for the following reasons: In honey, there is no time dependent depletion of residues as a result of pharmacokinetics, and residues, once present in honey, largely remain there or are degraded dependant on variables that are difficult to predict and not related to time. Therefore, the only feasible withdrawal period in honey is a 'zero' withdrawal period. Residue studies in honey according to VICH GL 56 are needed to support this 'zero' withdrawal period. These studies should show that there are no non-conforming residues (i.e. above the MRL) under conditions of good bee keeping practice.

6. Applications for authorisations for biological veterinary medicinal products

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 [4]. 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 allowed for all biologicals, independently of limited market status. In terms of limited market applications, the same data requirement options as for pharmaceutical products (see chapter 5.1.) apply for biological limited market applications.

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

7. 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*".

8. 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

[4] A distinction between chemical-like and chemical unlike biologicals, as laid out for the MRL authorisation, is not made in the context of product marketing authorisation.

https://ec.europa.eu/food/animals/health/veterinary-medicines-and-medicated-feed/imp-regs-2019_en

2. Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, repealing Council Regulation (EEC) No 2377/90 and amending Directive 2001/82/EC of the European Parliament and of the Council and Regulation (EC) 726/2004 of the European Parliament and of the Council http://ec.europa.eu/health/files/eudralex/vol-5/reg_2009-470/reg_470_2009_en.pdf

3. 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 https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:276:0033:0079:en:PDF

4. Commission Regulation (EU) 2017/880 of 23 May 2017 laying down rules on the use of a maximum residue limit established for a pharmacologically active substance in a particular foodstuff for another foodstuff derived from the same species and a maximum residue limit established for a pharmacologically active substance in one or more species for other species, in accordance with Regulation (EC) No 470/2009 of the European Parliament and of the Council https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0880&from=EN

5. Commission Regulation (EU) 2018/782 of 22 May 2018 establishing the methodological principles for the risk assessment and risk management recommendations referred to in Regulation (EC) No 470/2009 https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32018R0782&from=EN

6. CVMP and VICH safety and residues guidelines, available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000192.jsp&mid=WC0b01ac058002dd31:

   - CVMP 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)
   - CVMP Guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-Rev.1)
   - CVMP Guideline on user safety of topical administered products (EMEA/CVMP/SWP/721059/2014)
   - CVMP Note for guidance for the assessment of the effect of antimicrobial substances on dairy starter cultures (EMEA/CVMP/276/99-FINAL)
   - CVMP Note for guidance on the establishment of maximum residue limits for minor animal species (EMEA/CVMP/153a/97-FINAL)
   - CVMP Note for guidance on the establishment of maximum residue limits for Salmonidae and other fin fish (EMEA/CVMP/153b/97-FINAL)
   - CVMP Note for guidance on the risk analysis approach for residues of veterinary medicinal products in food of animal origin (EMEA/CVMP/187/00-FINAL).
   - VICH GL6: Environmental Impact Assessment (EIAs) for Veterinary Medicinal Products – Phase I (CVMP/VICH/592/98-FINAL)

- VICH GL22: Studies to evaluate the safety of residues of veterinary drugs in food: reproduction testing (CVMP/VICH/525/2000)
- VICH GL23: Studies to evaluate the safety of residues of veterinary drugs in food: genotoxicity testing (CVMP/VICH/526/2000)
- VICH GL28: Studies to evaluate the safety of residues of veterinary drugs in food: carcinogenicity testing (CVMP/VICH/645/2001 Rev.1)
- VICH GL31: Studies to evaluate the safety of residues of veterinary drugs in food: repeat-dose (90 days) toxicity testing (CVMP/VICH/484/2002)
- VICH GL32: Studies to evaluate the safety of residues of veterinary drugs in food: developmental toxicity testing (CVMP/VICH/485/2002)
- VICH GL33: Studies to evaluate the safety of residues of veterinary drugs in human food: general approach to testing (EMEA/CVMP/VICH/486/02-Rev.2)
- VICH GL36: Studies to evaluate the safety of residues of veterinary drugs in food: General approach to establish a microbiological ADI (EMA/CVMP/VICH/467/2003)
- VICH GL37: Studies to evaluate the safety of residues of veterinary drugs in human food: repeat-dose (chronic) toxicity testing (CVMP/VICH/468/03-FINAL)
- VICH GL38: Environmental Impact Assessment for Veterinary Medicinal Products – Phase II (CVMP/VICH/790/03-FINAL)
- VICH GL46: Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: metabolism study to determine the quantity and identify the nature of residues (EMA/CVMP/VICH/463072/2009)
- VICH GL47: Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: laboratory animal comparative metabolism studies EMA/CVMP/VICH/463104/2009)
- VICH GL48 (R): Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: marker residue depletion studies to establish product withdrawal periods
- 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)
- 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)
- 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)