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Safety and residue data requirements for the establishment of Maximum Residue Limits in minor species

Draft

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This guideline replaces the CVMP Guideline on safety and residue data requirements for veterinary medicinal products intended for minor uses or minor species/ limited market (EMEA/CVMP/SWP/66781/2005-Rev.2) regarding MRL applications.

Comments should be provided using this template. The completed comments form should be sent to vet-guidelines@ema.europa.eu

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Executive summary

Commission Regulation (EU) 2018/782 establishing the methodological principles for the risk assessment and risk management recommendations referred to in Regulation (EC) 470/2009 mentions the possibility of reduced data requirements for MRL applications for a substance for use in minor species.

The general aim of this guideline is to define acceptable requirements for MRL applications for pharmacologically active substances intended for use in minor species.

When MRLs have not been previously established for another species (full application), the standard safety data requirements can generally not be reduced for minor species. Data requirements needed to establish a health-based guidance value are set out in Commission Regulation (EU) 2018/782. Some residue data requirements may be reduced in relation to the total residue studies and to the analytical method.

When MRLs have already been established for one species, residue depletion studies may be waived for subsequent minor species (extension) applications under certain conditions.

Regarding the establishment of MRLs in honey, residue studies are required.

Regarding biological substances, flexibility is already considered in standard applications for major species. No data reductions are identified for minor species. A case by case approach is considered appropriate.

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).

Commission Regulation (EU) 2018/782 establishing the methodological principles for the risk assessment and risk management recommendations referred to in Regulation (EC) 470/2009 mentions the possibility of reduced data requirements for MRL applications for a substance for use in minor species.

It is the intention of this guideline to provide clear guidance on the circumstances under which data requirements can be reduced for MRL applications for minor species, to facilitate the applicant's work for estimating the required resources for such applications and preparing the application dossier and to provide for 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 Maximum Residues Limit (MRL) applications for minor species.

As a general principle, the CVMP and VICH relevant guidelines concerning safety and residues are also applicable to pharmacologically active substances intended for use in minor species.

3. Definitions

Minor/Major species

Definitions for minor/major species in the context of assessment of Maximum Residue Limits (MRL) under Regulation (EC) No 470/2009 are provided in Commission Regulation (EU) 2017/880 [Article 2 (3,4)].

According to Article 2 of Commission Regulation (EU) 2017/880 'major species' are defined as cattle, sheep for meat, pigs, chicken including eggs, and Salmonidae, whereas 'minor species' means any species other than major species.

Chemical-like biologicals

According to Commission Regulation (EU) 2018/782, a biological substance is chemical-like insofar as it could be produced by chemical synthesis and so presents similar concerns to chemical substances and can be expected to leave residues in the same way as chemical substances.

Chemical-unlike biologicals

According to Commission Regulation (EU) 2018/782, a biological substance is chemical-unlike insofar as being more complex than chemically synthesised pharmacologically active substances and so may contain multiple chemical types whose residues may generally be cells, amino acids, lipids, carbohydrates, nucleic acids and their breakdown products.

Extension of MRL

According to Commission Implementing Regulation (EU) 2017/12, an application or a request for the extension of existing MRLs to other animal species or other food commodities shall consist of an application or request form and a residue file. EMA may request safety data if the risk assessment performed with regard to the establishment of the existing MRL is not applicable to the extension proposed.

Applicants who wish to extend an existing MRL to a new animal species can submit an application for extension to EMA. If the additional species are minor species, according to Article 2 of Commission Regulation (EU) 2017/880 the approach described in section 5.2. is applicable.

Extrapolation of MRL

For extrapolation of MRLs by the CVMP there is a specific 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.

4. Legal basis

Regulation (EC) No 470/2009 lays down Union procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin. The information required for the establishment of MRLs by the European Union is set out in Commission Regulation (EU) 2018/782 establishing the methodological principles for the risk assessment and risk management

recommendations referred to in Regulation (EC) No 470/2009. This regulation mentions the possibility of reduced data requirements for MRL applications for a substance for use in minor species. The rules for extrapolation of MRLs are set out in 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.

5. Applications for Maximum Residue Limits for Minor Species

MRLs for minor species can be established following submission of: (a) an initial MRL application (no MRL is established for another species), (b) an application for extension of MRL (MRL for the concerned substance already established in another species or food commodity), (c) a request (by the Commission or a Member State) for extrapolation of MRLs to minor species according to Commission Regulation (EU) 2017/880. The possibility for extrapolation of MRLs will also be routinely considered by CVMP as part of its scientific risk assessment of initial and extension MRL applications, as referred to in article 5 of Regulation (EC) No 470/2009.

This guideline deals with data requirements for minor species when no MRL is established and with the extension of MRLs to minor species. The principles and requirements for extrapolation of MRLs are defined in Commission Regulation (EU) 2017/880 and are not addressed here.

In accordance with the provisions of Directive 2010/63/EU on the protection of animals used for scientific purpose, the conduct and design of *in-vivo* experimental studies should take account of 3Rs (replacement, reduction and refinement) principles.

5.1. MRL Applications for pharmacologically active substances for minor species with no MRL established for other species

5.1.1. Safety data requirements

Food derived from a minor species usually constitutes a small proportion of the diet of the average European consumer. It may, nevertheless, constitute a major portion of the intake of animal derived products in certain geographic areas or for certain subpopulations and therefore consumer safety must not be compromised.

The standard safety data requirements relating to effects that might occur after single and repeated exposure cannot be reduced for minor species. Data requirements needed to establish a health-based guidance value (HBGV; most often an ADI) are set out in Commission Regulation (EU) 2018/782.

It should be noted that for the safety evaluation, the data requirements are the same as for major species.

5.1.2. Residue data requirements

5.1.2.1. Total residue studies

Total residue (radiolabelled) studies will normally be required for pharmacologically active substances to identify the residue of concern in the minor species and to establish the ratio of the marker residue(s) to total residues, if necessary. Possible exemptions are substances where there is evidence that the only residues of concern are known and can be determined by validated analytical methods

(e.g. pharmacologically or microbiologically active component in case of pharmacological/microbiological ADI). For a novel compound intended for minor species, the requirement for a radiolabelled study could be waived on a case-by-case basis upon request when scientifically justified and supported by appropriate data. The applicant could request the CVMP to give scientific advice on this issue before the application is submitted to EMA. The advice of the CVMP may be based on the following considerations:

i. available absorption, distribution, metabolism and excretion (ADME) data (e.g. in laboratory species) that may be extrapolated to the minor species.

ii. if the novel compound belongs to a class of (veterinary or human) medicines for which it has been shown, in ADME studies in laboratory animals or other target species, that one or more of the following apply:

- such substances are not or are hardly metabolised,
- the metabolism of such substances is well known and comparable (within the chemical class and across species),
- structural differences between the novel compound and other substances of the same class of drugs are not indicative for a significantly different metabolism,

and:

- there is no indication of metabolites or degradation products of specific concern,
- the parent compound of such substances can be considered as a suitable marker residue for surveillance,
- the information on the metabolism of such substances provides an estimate of the ratio of marker to total residues, which can be used, for the calculation of the intake of total residues resulting from the proposed MRLs.

There are two other exemptions from the rule:

i. As detailed in the Note for guidance on the establishment of MRL for Salmonidae and other fin fish (EMEA/CVMP/153b/97 FINAL), in fish the parent compound is normally acceptable as a valid marker residue and radiolabelled studies are not required.

ii. Radiolabelled studies are also not required to establish an MRL for a substance in honey.

5.1.2.2. Marker Residue Studies

Where MRLs need to be established in the minor species, marker residue depletion studies in accordance with the requirements of Commission Regulation (EU) 2018/782 should be submitted.

5.1.2.3. Analytical Methods

The analytical method used in residue depletion studies need to be sufficiently validated. However, a reduced validation of the analytical method could be acceptable. The method should be validated in respect of the limit of quantification (LOQ) and, at least, for accuracy and precision. With regard to specificity, possible interference from matrix components and from chemically closely-related substances used in veterinary therapy should be investigated. Adequate storage and sample processing stability data should also be supplied. The availability of standards should be confirmed and contact details provided to allow an exchange of information, if necessary, between EU and national reference laboratory staff and the company.

5.2. MRL Applications for pharmacologically active substances for minor species where MRLs have been established for other species (Extensions)

5.2.1. Safety data requirements

It can be expected that, in most cases, a complete safety data package will have been assessed as part of the initial MRL evaluation, and that this would allow for a reduced data set to be considered when establishing MRLs in additional species, including minor species. However, the suitability of the safety data shall be assessed by comparing the metabolites produced in the laboratory animals to those seen in the target animals.

The outcome of the previous evaluation could have resulted in the establishment of an ADI and subsequently MRLs or a 'no MRL required' entry in Commission Regulation (EU) No 37/2010. It is also possible that no ADI was established, resulting in a 'no MRL required' entry in Commission Regulation (EU) No 37/2010. These substances are normally considered as safe, but the ’no MRL required‘ entry could be restricted to a particular route of administration, or have been intended only for minor species, and previous 'rules' had been applied, resulting in reduced data requirements for the safety package. In such instances, safety data may be required, depending on the application submitted.

For substances where the ADI or alternative limit have already been established, no additional safety data are required, as long as the metabolite profile in the two different species are comparable. An *in vitro* study might be sufficient to address this issue. The ADI that has already been determined can be used to establish MRLs in the minor species, together with the relevant residue data. However, when new relevant literature has been published since the establishment of the ADI, the applicant should include and evaluate this information in the data package.

5.2.2. Residue data requirements

For extension of MRLs from one species to another species, suitable pharmacokinetic and residue depletion data in the relevant food commodities and conducted according to VICH GL 46 and/or VICH GL 48 (R) should be considered. If the application for extension concerns the same food commodities and the residue depletion study was conducted according to current requirements, only data showing that metabolism in the new target species does not significantly differ from the previous species are necessary (thus indicating that residues produced in the new target species, like those produced in the original target species, reflect those produced in the laboratory animals). Also ratios of marker to total residues between the original target species and the new target species need to be similar. If other/additional food commodities are concerned and/or the available study data do not fit the requirements, appropriate residue depletion studies need to be conducted.

5.3. Establishment of MRLs for honey

The establishment of MRLs in honey requires residue studies. While the determination of a theoretical safe level in honey could, in principle, be calculated directly from the ADI or the portion of the ADI available. Current requirements for residue studies in honey are given in Commission Regulation (EU) 2018/782 and in VICH GL56. If no ADI is available for a substance, appropriate safety data are needed allowing to establish an ADI (see section 5.1.1).

Assessment of residues in honey is more complex than in mammalian or avian tissues. In honey, there is no time dependent depletion/elimination of residues as a result of pharmacokinetics (as in mammalian/avian tissues). Residues, once present in honey, largely remain there. Apart from possible chemical degradation of a substance in honey matrix over time, the main variable responsible for the level of residues at harvest time is the honey yield (dilution effect), which in large part depends on the

production site (geographical area) and weather conditions at flowering time. These variables are unpredictable and not directly related to a specifiable period of time. Therefore, the only feasible withdrawal period in honey is a 'zero' withdrawal period. Residue studies covering a reasonable range of commercial treatment conditions are needed to support the suitability of the MRL. These studies should show that there are no non-conforming residues (i.e. above the MRL) at 'zero' withdrawal period under conditions of good bee keeping practice.

5.4. MRL Applications for biological substances for minor species

Regulation (EC) No 470/2009 excludes from its scope active substances of biological origin intended to produce active or passive immunity or to diagnose a state of immunity. The MRL status of biological substances that do not fall into this category must be addressed in order to allow their use in veterinary medicinal products for use in food producing animals. Generally, standard data requirements identical to those that apply for chemical substances are required for chemical-like biological substances. The information required for the evaluation of chemical-unlike biological substances is assessed on a case-by-case basis as outlined in Commission Regulation (EU) 2018/782. When it is determined that no standard MRL assessment is required, a summary of the evaluation is published by EMA and the substance will be included in the 'list of biological substances considered as not requiring an MRL evaluation' (EMA/CVMP/572629/2019). A legal or regulatory definition to precisely distinguish between 'chemical-like' and 'chemical-unlike' is not currently available. Hence, the EMA considers the suitability of each application for a chemical-unlike biological substance as defined in Annex I.6 of Commission Regulation (EU) 2018/782 on a case by case basis upon submission of an application for inclusion of a substance in the above-mentioned list. A standard MRL evaluation including standard data requirements is required in case a substance is not considered eligible for the 'list of biological substances not requiring MRL evaluation'.

At the time of writing, due to the limited experience that has been gathered with consumer safety assessments of biologicals, and due to the fact that there is a case by case approach in place for chemical-unlike biologicals standard safety data requirements cannot be specified and consequently it is not possible to specify reduced requirements for minor species. A report as outlined in Annex I.7 of Commission Regulation (EU) 2018/782 is required to determine whether there is a need for an MRL evaluation and whether inclusion in the dedicated list is possible.

Where a previous assessment of a substance has been performed in relation to use in another species, this may negate the need for certain types of data to be provided in relation to subsequently proposed uses. Generally, no new information is required when it can be shown that the risk is identical to the risk previously identified in an assessment.

For chemical-like biologicals, the same requirements as for chemical substances apply.

6. 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/PDF/?uri=CELEX:32019R0006&from=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. Commission Implementing Regulation (EU) 2017/12 of 6 January 2017 regarding the form and content of the applications and requests for the establishment of maximum residue limits 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:32017R0012

7. 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 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 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 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)