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Guideline on safety and residue data requirements for veterinary medicinal products intended for minor use or minor species (MUMS)/limited market

Draft

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This guideline updates 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).

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30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5545
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Guideline on safety and residue data requirements for veterinary medicinal products intended for minor use minor species (MUMS)/limited market

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Executive summary

In order to stimulate the development of new veterinary medicines intended for minor uses or minor species (MUMS)/limited market the CVMP developed guidelines on data requirements for MUMS/limited market veterinary medicinal products for quality, safety and efficacy for pharmaceuticals and a guideline for immunologicals. These guidelines are intended to reduce data requirements where possible for products classified as MUMS/limited market while still providing assurance of appropriate quality, safety and efficacy and complying with the legislation in place and leading to an overall positive benefit-risk balance for the product.

These MUMS guidelines have now been reviewed and revised with the aim of updating the acceptable data requirements in light of experience gained and clarifying, where appropriate, the applicability of the MUMS data requirements. This draft revised guideline describes the data requirements regarding safety and residues for veterinary medicinal products classified as MUMS/limited market.

1. Introduction

For some time there has been considerable concern amongst all parties concerned with animal health in the EU about the lack of authorised veterinary medicinal products for minor uses and for minor species. The availability of safe and effective veterinary medicinal products for minor uses or minor species (MUMS)/limited market will improve both animal welfare, animal health and, in some cases, public health. The Agency at the behest of its Management Board began discussions and consultations on this increasing problem in 1998 and, since that time, the CVMP has worked on the matter and is active in initiatives to address the problem of lack of veterinary medicines.

One of the initial measures introduced by the CVMP was to review data requirements for veterinary medicinal products intended for MUMS, both for pharmaceuticals and immunologicals, and, if possible, to establish standards for demonstration of quality, safety and efficacy for these. A set of CVMP guidelines on data requirements for veterinary medicinal products intended for minor use minor species were finalised in 2006 to 2008 (EMEA/CVMP/QWP/128710/2004, EMEA/CVMP/SWP/66781/2005, EMEA/CVMP/EWP/117899/2004, EMA/CVMP/IWP/123243/2006).

Since then the Agency Policy for classification and incentives for veterinary medicinal products indicated for MUMS/limited markets was established and implemented on 1 September 2009 and updated in December 2014 (EMA/308411/2014). The policy is supported by a guidance document on the classification of veterinary medicinal products indicated for minor use minor species (MUMS) / limited market (EMA/CVMP/388694/2014) providing guidance for implementing the policy and the procedure and criteria for classification of products or applications as MUMS/limited market.

The policy is intended to stimulate the development of new veterinary medicines for minor species and for diseases occurring infrequently or in limited geographical areas in major species that would otherwise not be developed in the current market conditions. The guidelines on data requirements for products classified as MUMS/limited market are an integral part of the policy.

These guidelines are intended to reduce data requirements where possible for products classified as MUMS/limited market while still providing assurance of appropriate quality safety and efficacy and complying with the legislation in place and leading to an overall positive benefit-risk balance for the product.

These guidelines have now been reviewed and revised with the aim of updating the acceptable data requirements in light of experience gained and clarifying, where appropriate, the applicability of the MUMS data requirements.

It is the intention to provide clear guidance under which circumstances data requirements can be reduced for MUMS/limited market products to facilitate the applicant's work for estimating the required resources for a MUMS/limited market application and preparing the application dossier and provide for predictability. However, it is recognised that this is not always feasible as not all possible scenarios can be addressed in a general guidance document.

Furthermore, the specific requirements will depend on the data and knowledge available, e.g. there may be scope for reductions if a product has been authorised already for a major species or major use or an MRL has been established for a major species, or if a product concerns an active substance belonging to a well-known class of substances. However, for products containing entirely new active substances, novel therapy products or products representing first in class the possibilities for data reduction are likely to be limited. Similarly, for products presenting a specific risk, e.g. for products containing an antimicrobial or vaccines containing GMOs, the possibility for reducing data requirements will be severely limited in the area related to addressing the risk, i.e. adequate data to justify the indication and establish the appropriate dosage regimen or data to ensure safe and efficacious use of such a vaccine will need to be established, even if the product is classified as MUMS/limited market.

The general aim of this guideline is to define acceptable data requirements for safety and residues documentation for veterinary medicinal products intended for minor uses or minor species. In this context, data requirements for the demonstration of safety will be influenced to a certain extent by the active substance/product type and whether or not the product is/has been authorised in a related major species for the same or a similar route of administration. It follows that where an active substance/product is or has been authorised for the same or a similar route of administration in a major species, information relating to use in that species may be used in support of the application and, where justified, this may obviate the need for certain toxicity studies. For novel active substances and for those where limited information is available relating to their use in any animal species, comprehensive toxicity information will be required.

The guidance provided in this document is general. Applicants are advised to request scientific advice on their individual data package to confirm the precise requirements for their specific application.

2. Scope

The objective of this guideline is to clarify the requirements as follows:

- The data requirements for minor species for an MRL application with no MRL established for other species.
- The data requirements for minor species for an MRL application where an MRL has been established for other species.
- The data requirements for a marketing authorisation application for a minor food producing species.
- The data requirements for a marketing authorisation application for a minor non-food producing species.
- The data requirements for a major species for a marketing authorisation application for a limited market.

As a general principle, the CVMP and VICH guidelines concerning safety and residues are applicable to minor use/minor species products.

3. Definitions

Definitions are provided in the Revised policy for classification and incentives for veterinary medicinal products indicated for minor use minor species (MUMS)/limited market (EMA/308411/2014).

Minor species: There is no legislative definition in the EU for major or minor species.

Major species have been defined by the CVMP as follows:

Major food-producing species:

- cattle (dairy and meat animals);
- sheep (meat animals);
- pigs;
- chickens (including laying hens);
- salmon[1].

Major companion animal species:

- cats;
- dogs.

All other animal species, which are not considered major, are as a consequence, by default, classed as minor species.

Minor use: Minor use in a major species is generally considered as the use of veterinary medicinal products for the treatment of diseases that occur infrequently or occur in limited geographical areas and thus are indicated for a smaller market sector.

Limited market: A market for a veterinary medicinal product that is limited in size due to the product being indicated for a disease or condition that represents a minor use in a major species or that occurs in a minor species.

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. This Regulation replaced Council Regulation (EEC) No 2377/90 and the Annexes that contained the list of allowed and non-allowed substances were entered into a new Commission Regulation (EU) No 37/2010 of 22 December 2009. The information required for the establishment of MRLs by the European Union is set out in Volume 8 of The Rules Governing Medicinal Products in the European Union.

Requirements for safety testing for a marketing authorisation application are laid down in Article 12 of Directive 2001/82/EC, and are specified in Annex I of Directive 2001/82/EC, Title I for pharmaceuticals, as amended by Directive 2009/9/EC.

[1] Salmon should be considered a major species, however other species of the *Salmonidae* family such as rainbow trout should be considered minor species. The term salmon is understood in this context as Atlantic salmon (*Salmo salar*).

One of the intentions of the legislation in place for the authorisation of veterinary medicines as laid down in the preamble of Directive 2001/82/EC, preamble points No. 9 and 10 of Directive 2004/28/EC, is to facilitate the authorisation of certain veterinary medicinal products:

"(9) The costs of research and development to meet increased requirements as regards the quality, safety and efficacy of veterinary medicinal products are leading to a gradual reduction in the range of products authorised for the species and indications representing smaller market sectors."

"(10) The provisions of Directive 2001/82/EC also need, therefore, to be adapted to the specific features of the sector, particularly to meet the health and welfare needs of food-producing animals on terms that guarantee a high level of consumer protection, and in a context that provides adequate economic interest for the veterinary medicinal products industry."

This is also reflected in Annex I of Directive 2001/82/EC under Introduction and General Principles.

"(10) In cases of applications for marketing authorisations for veterinary medicinal products indicated for animal species and indications representing smaller market sectors, a more flexible approach may be applicable. In such cases, relevant scientific guidelines and/or scientific advice should be taken into account."

5. MRL Applications for minor species with no MRL established for other species – General requirements

5.1. 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.

It was concluded that the standard safety data requirements relating to any effects that might occur after single and repeated exposure could not be reduced for minor species.

5.1.1. Establishment of the ADI and MRL in a minor species

Table 1 presents the data requirements for testing the safety (i.e. pharmacology and toxicology) of those substances that are used in minor food-producing species and for the establishment of a MRL, where MRLs have not been established for use in a major food-producing species. It should be noted that for the safety evaluation, the data requirements are broadly the same as for major species.

5.1.2. Pharmacological data

Pharmacological data for a minor species must provide sufficient information for an assessment of the pharmacodynamic effects in order to establish whether a pharmacological ADI is required. Pharmacological studies may assist in the understanding of toxicological phenomena or show pharmacological effects in the absence of toxicological responses. Thus, if there are no human data, details of pharmacodynamic studies in laboratory animals are required. However, an abbreviated dataset not including pharmacodynamic studies may be considered, depending on the substance under consideration, but the absence of data must be satisfactorily justified with a summary of anticipated pharmacodynamic effects.

Pharmacokinetic studies in laboratory animals, and if available, human data should be submitted for the assessment of the fate of the substance. These are fundamental data that are required for selection of appropriate species for toxicity studies and the establishment of an ADI and MRLs.

5.1.3. Toxicological data

Toxicological data are required for an assessment of adverse effects and to establish a toxicological ADI and the dataset must be sufficient to establish this. CVMP/VICH guidelines should be followed with regard to the choice of the studies required by this guideline and the toxicological tests themselves should be conducted in accordance with the relevant OECD or other internationally recognised guidelines. Any deviation should be adequately justified.

5.2. Residue data requirements

5.2.1. Total residue studies

Total residue (radiolabelled) studies will normally be required for most veterinary 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 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 substitute 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 of which it has been shown, in ADME studies in laboratory animals or other target species, that one or more of the following apply:

- such medicines are not or hardly metabolised,
- the metabolism of such medicines is well known and comparable,
- 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 of specific concern,
- the parent compound of such medicines can be considered as a suitable marker residue for surveillance,
- the information on the metabolism of such medicines provides an estimate of the ratio of marker to total residues, which can be used, for the calculation of the intake of residues resulting from the proposed MRLs.

There are two other exemptions from the rule. 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. Radiolabelled studies are also not required to establish an MRL for a substance in honey.

5.2.2. Marker Residue Studies

Where MRLs need to be established in the minor species, marker residue depletion studies in accordance with the requirements of Volume 8 should be submitted.

5.2.3. Regulatory Analytical Methods

For the purposes of monitoring residues, there is also a need for a regulatory analytical method for minor species. However, a reduced validation of the proposed regulatory analytical method could be acceptable. The method should be validated in respect to the "limit of quantification" and, at least, for accuracy and precision at the level of the MRL and half the MRL. 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.

5.3. Establishment of MRLs for honey

The establishment of MRLs in honey requires residue studies. While the calculation of a theoretical safe level in honey could in principle be done directly from the ADI or the portion of the ADI available, an MRL can however not be set without knowing the residue concentrations that are typically occurring in practice. Current requirements for residue studies in honey are given in Volume 8 of the Rules Governing Medicinal Product in the European Union. The VICH is also expected to publish draft guidance on data requirements for the establishment of MRLs in honey during 2016.

Assessment of residues in honey is more complex than in mammalian or avian tissues. In honey matrix, 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 parts 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 this "zero" withdrawal period. These studies should show with reasonable statistical certainty that there are no non-conforming residues (i.e. above the MRL) under conditions of good bee keeping practice.

6. MRL Applications for minor species where MRLs have been established for other species – General requirements

6.1. Safety data requirements

For substances where MRLs have already been established for other species, the safety data must have been submitted and evaluated. The outcome of the evaluation could result in the establishment of the ADI and subsequently MRLs. It is also possible that no ADI was established resulting in a "no MRL required" entry in Regulation 37/2010. These substances are normally considered as safe but the "no MRL required" entry could be restricted to a particular route of administration. In such instances, safety data may be required depending on the application submitted.

6.1.1. Establishment of the ADI and MRL in a minor species

For substances where the ADI has already been established, no additional safety data are required. The ADI that has already been determined can be used to establish MRLs in the minor species together with the relevant residue data.

In situations where no ADI has been determined for a substance but with a 'no MRL required' entry for other species, possibly with a restriction (e.g. For topical use only), if the MRL that has been sought is without any restriction, then safety data as set out in section 4 above will be required.

6.2. Residue data requirements

Once the need for the establishment of MRLs for the minor species has been identified, the first point to consider is whether extrapolation of MRLs established in other species to the minor species is possible. The criteria for extrapolation are set out in 6.2.1 below. If extrapolation is not possible, then residue data as set out in section 4.2 above are required.

6.2.1. Extrapolation of MRLs from major to minor species

Previously, much effort by the CVMP regarding availability of veterinary medicines focussed on extrapolation of existing MRLs from major species to minor species and significant progress has been made in this area and guidance has previously been developed (CVMP Note for Guidance on the Establishment of Maximum Residue Limits for Minor Animal Species, EMEA/CVMP/153a/97 and Note for Guidance on the Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of Animal Origin, EMEA/CVMP/187/00-FINAL). The principle of extrapolation received legal backing when it was incorporated in Article 5 of Regulation (EC) 470/2009. The CVMP now actively considers whether extrapolation would be possible to other species as part of its MRL evaluations.

Since the adoption of Regulation (EC) 470/2009, the CVMP has worked to revise its principles on extrapolation of MRLs and it is anticipated that a new approach will be published for consultation during 2016.

The guidance as described in document EMEA/CVMP/187/00-FINAL indicates that in cases where identical or only slightly different MRLs exist in major species, such as cattle (or sheep), pigs and chickens (or poultry), extrapolations to minor species are possible on the basis of very limited information. When extrapolating the MRL to a minor species, it is not considered necessary that a fully validated analytical method is provided. It is normally sufficient to demonstrate that the method developed for the major species is also applicable in the minor species. The marker residue should exist in the target species for extrapolation, for which reason a limited depletion study is required.

Where identical or very similar MRLs have been set for three major species from different animal classes (ruminants, monogastrics and poultry), based on specific residue data, confirming a similar consumer exposure in relation to these species, it can be assumed that the exposure assessment and consequently the risk characterisation on the basis of same/similar MRLs for further species beyond the animal classes concerned would be similar.

i. MRLs should be allowed to be extrapolated within classes of animals. Thus, it should be possible to extrapolate from:

Species for which MRLs have been set	**Extrapolations to:**
Major ruminant (meat)	All ruminants (meat)
Major ruminant milk	All ruminant milk
Major monogastric mammal	Extrapolation to all monogastric mammals
Chicken and eggs	Poultry and poultry eggs
Salmonidae	All fin fish
Either a major ruminant or a major monogastric mammal	Horses

ii. If identical MRLs were derived in cattle (or sheep), pigs and chicken (or poultry), which represent major species with different metabolic capacities and tissue composition, the same MRLs can also be set for ovine, equidae and rabbits, which means an extrapolation is considered possible to all food-producing animals except fish. Considering the CVMP Note for guidance on the establishment of MRLs for *Salmonidae* and other fin fish (EMEA/CVMP/153b/97-FINAL), which already allows an extrapolation from MRLs in muscle of a major species to *Salmonidae* and other finfish provided that the parent substance is acceptable as marker residue for the MRL in muscle and skin, MRLs can be extrapolated to all food-producing animals.

The applicant should justify that available analytical methods are suitable for monitoring residues in edible tissues and products of all food-producing animals as outlined above.

iii. In cases where MRLs were established in cattle (or sheep), pigs and chickens (or poultry), which were slightly different, extrapolation to further species as outlined under ii) could also be possible. The most relevant set of MRLs for the extrapolation should be chosen on the basis of the amount of residues likely to be ingested or the most conservative MRL. The applicant should demonstrate that analytical methods are available for monitoring residues in edible tissues and products of all food-producing animals as outlined above.

Further advice is given in the 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).

7. Marketing authorisation applications for food producing minor species – General requirements

7.1. Safety data requirements

The requirements for Marketing Authorisations for food producing species as given in the Directive 2001/82/EC as amended and the CVMP/VICH Safety guidelines were considered and reductions in the safety data requirements have been identified.

7.1.1. Tabulated minimum datasets

Table 2 presents the data requirements for safety testing (i.e. pharmacology and toxicology) for a Marketing Authorisation for minor food producing species where there are MRLs established for the active ingredients in a minor food producing species, in accordance with Part 3A Safety Testing as laid

down in Annex I of Directive 2001/82/EC, as amended by Directive 2009/9/EC. As substances with MRLs are likely to have a published Summary Report (SR) or European Public MRL Assessment Report (EPMAR), information from these publications may be used in support of the pharmacology and toxicology part of the application dossier.

7.1.2. Marketing Authorisation applications and the use of MRL summary report or EPMARs in accordance with Directive 2001/82/EC, as amended

It should be noted that Directive 2001/82/EC, as amended, permits Marketing Authorisation applications made in accordance with Article 13a, to submit the published EMA/CVMP SR/EPMAR as published literature, particularly for the safety tests, thus allowing an exemption for pharmacological and toxicological data. Article 13a refers to applications made on the basis of "well-established use" and permits the submission of scientific literature in place of study data. Therefore, when an MRL has been established for a substance for a major or minor food producing species, it will be possible for the Marketing Authorisation applicant to submit the EMA/CVMP MRL SR/EPMAR as part of the published literature submitted.

7.1.3. Pharmacological data

Pharmacological studies in laboratory animals and the target species can be replaced by cross reference to the target species studies submitted in Part 4 of the dossier by means of a summary of any observed effects in the pharmacodynamic studies and a summary of the pharmacokinetics to include absorption, distribution, metabolism and excretion (ADME). The pharmacokinetics of the active substance following oral exposure to residues will have been considered as part of the MRL application and cross reference can be made to the EMA/CVMP MRL SR/EPMAR.

7.1.4. Toxicological data

Toxicological data are required for the evaluation of user safety and the assessment of adverse effects. For example, the data set must be adequate for the evaluation of possible adverse effects to fertility or reproduction. It should also consider potential problems associated with administration, such as exposure by inhalation or dermal contact and accidental self-injection. The omission of studies should be adequately justified.

Where available, 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. The toxicology of the active substance following oral exposure to residues will have been considered as part of the MRL application and cross reference can also be made to the EMA/CVMP MRL SR/EPMAR. See the user safety section below for further guidance.

7.1.5. User safety assessment

A user risk assessment from administration of the product and risk management proposals must be submitted for all applications. The requirements of the user safety guideline (EMEA/CVMP/543/03-Rev.1) should be applied. This guideline allows for consideration of (low) exposure frequencies. This assessment should include a discussion of the effects found in the pharmacological and toxicological data and relate this to the type and extent of human exposure to the product with a view to formulating appropriate user warnings.

7.1.6. Environmental safety

Environmental safety requirements for minor species and minor use are described in the questions 4 and 5, respectively, of the CVMP/VICH Phase I guidance as given in CVMP/VICH/592/98-FINAL. This guideline came into force in July 2000, and in view of the modification of the legislation since then, the following is to be considered for minor species:

An environmental risk assessment (ERA) for minor species is not required in the case where it is available for a major species, provided that: 1) the minor species is reared under similar conditions as the major species, and the primary environmental release of the VMP used for minor and major species is to the same environmental compartment, e.g. soil or water[1]; and 2) the VMP is administered by the same route and the total dose administered to the minor species is no greater that used in the major species. In that case the ERA conclusions from the major species also apply to the minor species.

[1] If a VMP for major species, for example, is approved for stabled husbandry with manure as the primary environmental entry point, the same VMP used for minor species in aquaculture need to undertake an ERA.

7.2. Residue data requirements

7.2.1. Withdrawal periods for minor species

Whereas the MRL refers to the active chemical substance itself, the withdrawal period refers to, and is dependent on, the specific marketing formulation of a veterinary medicinal product (VMP) and dosing regimen. Each product has to be considered on its own merits. Current guidelines on setting withdrawal periods do not differentiate between minor and major species. Data requirements are practically the same (see Table 4) except in some of the following cases.

The VICH is expected to publish draft guidance on residue studies in aquatic species and honey during 2016.

7.2.1.1. Identical products

In case of the same VMP with the same MRL in the major/minor species, following an approach similar to the approach for extrapolation of MRLs could be considered, i.e. no residue depletion studies may be required in the minor species. In accordance with the approach accepted for extrapolation of MRLs, an extrapolation of withdrawal periods should be possible from cattle/sheep to other ruminants, from chicken other avian species, from Salmonidae to other fin fish etc. Exemptions are products having a potential to leave local residues (in particular injectable products administered intramuscularly and subcutaneously as well as dermal applications). In this case, information on the behaviour of residues at the site of administration needs to be assessed before the withdrawal period is extrapolated, limited residue depletion studies (e.g. at 2 time points, one just before the reference withdrawal period and one after it) or alternatively an uncertainty (safety) factor to compensate for uncertainties in the extrapolation could be considered (multiplication of the withdrawal period in the major species by an uncertainty factor of 1.5). Use of an uncertainty factor would only be appropriate if the dose and volume of injection are no greater than that administered in the major species.

7.2.1.2. Products with identical active ingredient but with different formulation/different dosing regimen/routes of administration

Differences in the pharmaceutical composition can have a considerable impact on pharmacokinetic properties and route-to-route or dose-to-dose extrapolations of withdrawal periods might not be

feasible, particularly if injectable formulations are involved. With respect to non-identical products, a more cautious approach is necessary and products need to be assessed on a case-by-case basis.

In the case of a multiple administrations of a product, it would be important to know the accumulation profile of the active substance or the marker residue in the minor species. Normally, some experimental information in the minor species will be required to support the withdrawal period. An approach based on limited residue data could be acceptable: pharmacokinetic studies demonstrating similar profiles could provide useful data to support an extrapolation of withdrawal periods between major/minor species. Setting of a withdrawal period in the minor species based on overall pharmacokinetic parameters (e.g., plasma elimination half-live) could be an option for certain compounds (e.g., compounds distributed mainly in extracellular fluids/plasma only).

In the absence of residue data, use of an uncertainty (safety) factor to compensate for uncertainties in the extrapolation could be considered (multiplication of the withdrawal period in the major species by a certain factor, e.g. 1.5) if it is clear that the new formulation is essentially similar to the original formulation and is used at or below the dose used for the original formulation with the same route of administration.

When the product for the minor species is to be used at a significantly higher dose level/dosing regimen, conventional residue studies will be required to confirm the withdrawal period. Where the product for the minor species is intended for injection (intramuscular or subcutaneous), residue data at the injection site will also be needed. Likewise, for veterinary medicinal products for dermal applications, local residues in edible tissues below the site of administration need to be investigated.

For residue studies in the minor species the analytical method used in a residue depletion study must be validated in line with VICH GL49 (EMA/CVMP/VICH/463202/2009) otherwise the study itself would not be valid (see below at 7.2.1.4 and also Table 5).

7.2.1.3. Products not authorised previously for major species

Residue studies according to guidelines are normally required for veterinary medicinal products for a minor species where previously no similar product was authorised for a major species.

Extrapolation may be possible if a residue study is available for a minor species in the same category conducted and evaluated according to the guidelines (e.g, turkeys to ducks) (Pharmacokinetic parameters should be comparable, pharmaceutical form, route of administration and dosing regimen should also be the same).

7.2.1.4. Analytical methods (in residue studies supporting withdrawal periods in minor species)

The analytical method used in a residue depletion study must be validated in line with VICH GL49 (EMA/CVMP/VICH/463202/2009) otherwise the study itself would not be valid.

7.2.1.5. Withdrawal periods for compounds with a 'no MRL required' entry

Many compounds with a 'no MRL required' entry have been placed there based on consideration of quick metabolism/elimination of residues and/or limited use (see Annex II criteria in the 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] Appendix 1. For such compounds, no MRL is available on which to base the withdrawal period. For many compounds with a 'no MRL required' entry there is an established ADI, but there are several compounds for which there is none (e.g. xylazine, levomethadone). For compounds with an ADI, the ADI can serve as a reference point for the

withdrawal period. A complication inherent in the ADI approach is, however, that the ADI often relates to total drug derived residues or a combination parent compounds plus metabolites. Consequently, in a strict sense, a withdrawal period based on the ADI would necessitate residue studies for more than a single component, i.e. normally total residue (radiolabelled) studies, which are extremely complex and costly. A request for total residue (radiolabelled) studies for setting withdrawal periods is normally not reasonable or warranted for compounds fulfilling a 'no MRL required' criteria. In this case, it would be sufficient to estimate a withdrawal period based on depletion data for the most relevant residue component in the tissue with the slowest depletion rate (could be the parent compound and/or major metabolite). Supporting information allowing the estimation of food basket residues should be available from the MRL procedure (residue distribution data between tissues, ratios between residue components in tissues). The same consideration applies to compounds with no ADI where an alternative exposure limit (e.g. Tolerable dietary intake) may serve as reference point for the withdrawal period.

Withdrawal periods for compounds with a 'no MRL required' entry for which an ADI has been set, it would be reasonable to use an uncertainty factor (e.g. 1.5) for extrapolating the withdrawal period for minor species from major species.

8. Marketing authorisation applications for non-food producing minor species – General requirements

8.1. Safety data requirements

The requirements for Marketing Authorisations for non-food producing species as given in Annex I to Directive 2001/82/EC as amended by Annex I to Directive 2009/9/EC, already foresees exemptions for non-food producing species therefore very limited reductions in data requirements were identified. The specific safety data requirements are listed in Table 3.

8.1.1. Tabulated minimum datasets

Table 3 presents the data requirements for safety testing (i.e. pharmacology and toxicology) for a Marketing Authorisation for non-food-producing species, in accordance with Part 3A Safety Testing as laid down in Annex I Directive 2001/82/EC as amended by Directive 2004/28/EC with the exception of environmental safety requirements and in accordance with the CVMP/VICH Safety guidelines.

The data set for major non-food producing species as required by the legislation is already reduced in comparison to that of the food producing species, and therefore only limited reduction of the data set can be made.

8.1.2. Marketing Authorisation applications and the use of MRL SR or EPMARs in accordance with Directive 2001/82/EC, as amended

It should be noted that the amending Directive 2004/28/EC permits Marketing Authorisation applications made in accordance with Article 13a, to submit the published EMEA/CVMP MRL SR/EPMAR as published literature, particularly for the safety tests, thus allowing an exemption for pharmacological and toxicological data. Article 13a refers to applications made on the basis of "well-established use" and permits the submission of scientific literature in place of study data. Therefore, when an MRL has been established for a substance for a major or minor food producing species, it will be possible for the Marketing Authorisation applicant to submit the EMEA/CVMP MRL SR or EPMAR as part of the published literature submitted. Therefore MRL SR/EPMAR can be submitted as part of a

bibliographic application in accordance with the amending Directive 2004/28/EC even though the Marketing Authorisation may be for non-food producing species.

8.1.3. Pharmacological data

Pharmacological studies in laboratory animals and the target species can be replaced by cross reference to the target species studies submitted in Part 4 of the dossier by means of a summary of any observed effects in the pharmacodynamic studies and a summary of the pharmacokinetics to include absorption, distribution, metabolism and excretion (ADME). Absence of studies in laboratory animals must be satisfactorily justified.

8.1.4. Toxicological data

Toxicological data are required for the establishment of user safety and the assessment of adverse effects (e.g. possible adverse effects to fertility or reproduction). It should also consider potential problems associated with administration, such as exposure by inhalation or dermal contact and accidental self-injection. The omission of studies should be adequately justified.

Where appropriate, 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.

8.1.5. User safety assessment

A user risk assessment of toxicity, hazard, and exposure from administration of the product and risk management proposals must be submitted for all applications. The requirements of the user safety guideline (EMEA/CVMP/543/03-Rev.1) should be applied. This guideline allows for consideration of (low) exposure frequencies. This assessment should include a discussion of the effects found in the pharmacological and toxicological data and relate this to the type and extent of human exposure to the product with a view to formulating appropriate user warnings.

8.1.6. Environmental safety

Environmental safety requirements should be addressed by referring to the CVMP/VICH Phase I guidance as given in CVMP/VICH/592/98-FINAL.

9. Summary tables of data requirements

Table 1 Data Requirements for Safety Testing for establishment of MRLs for Minor Food-Producing Species (when there are no MRLs established in a major food-producing species).

Table 2 Data Requirements for Safety Testing for a Marketing Authorisation for Minor Food-Producing Species (where MRLs are established for the active ingredient in a major/minor food-producing species)

Table 3 Data Requirements for Safety Testing for a Marketing Authorisation for Non-Food-Producing Species

Table 4 Current data requirements for residues studies for MRL and withdrawal periods

Table 5 Current data requirements for analytical methods

560 **Table 1 Data requirements for safety testing for establishment of MRLs for minor food-**
561 **producing species (when there are no MRLs established in a major food-producing**
562 **species).**

Regulation (EC) No. 470/2009	Standard data requirements (as given in Volume 8 October 2005)	Minimum dataset for minor food-producing species
A Safety file		
A2. Pharmacology		
2.1 Pharmacodynamics	Details of pharmacodynamic studies in laboratory animals in the absence of human data	Details of pharmacodynamic studies in laboratory animals in the absence of human data may be necessary on a case by case basis, depending on the substance under consideration. A minimum dataset not including pharmacodynamic studies must be justified.
2.2 Pharmacokinetics	Details of pharmacokinetic studies in laboratory animals, and if available, human data	Same criteria apply.
A3. Toxicological studies		
3.1 Single dose toxicity	• Not required. • Studies may be submitted where they exist in the study archive or in published literature. Cross refer to any other acute toxicity studies (e.g. user safety studies)	Same criteria apply.
3.2 Repeat dose toxicity	• 90 day study (OECD 408, 409) • 2 species, 1 must be non-rodent • Oral administration • Chronic toxicity study[2] (OECD 452)	Same criteria apply.
3.3 Tolerance in the target species	Cross-refer to existing study reports of tolerance testing.	Not required.
3.4 Reproductive toxicity including developmental toxicity		
3.4.1 Study of the effects on reproduction	2-generation study in at least 1 species usually rodent (oral route) (OECD 416)	Same criteria apply.
3.4.2 Study of developmental toxicity	Developmental toxicity: tiered approach – VICH GL32[3] (OECD 414)	Same criteria apply.
3.5 Mutagenicity	Testing strategy in accordance with current state of scientific knowledge (VICH GL23R) The standard battery consists of the following three tests: i) bacterial gene mutation test ii) A cytogenetic test for chromosomal damage (the *in vitro* metaphase chromosome aberration test or in	Same criteria apply.

[2] The 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) indicates that most veterinary drugs will need to be tested for the adverse consequences of chronic exposure, as there is a potential for consumers to be exposed repeatedly throughout their lifetime. However, the guideline does not preclude the possibility of alternative approaches that may offer an equivalent assurance of safety, including scientifically based reasons as to why chronic toxicity testing may not need to be provided

[3] As given in Volume 8

Regulation (EC) No. 470/2009	Standard data requirements (as given in Volume 8 October 2005)	Minimum dataset for minor food-producing species
	vitro micronucleus test), or an in vitro mouse lymphoma tk gene mutation assay iii) An in vivo test for chromosomal effects using rodent haematopoietic cells	
3.6 Carcinogenicity	Long-term animal carcinogenicity bioassays will usually be required for substances to which human beings will be exposed when any of the following criteria apply: • where structure-activity relationships indicate a close chemical analogy with known carcinogens; • where findings in toxicity studies have identified potentially pre-neoplastic lesions or are indicative of neoplasia. • where mutagenicity testing produced results indicating a possibility of carcinogenic effects; • (VICH GL 28) (OECD 451 & 453)	Same criteria apply.
A.4 Studies of Other Effects		
4.1 Immunotoxicity	• If immunological effects in repeat dose studies are observed, additional studies are required • Additional studies in accordance with current state of scientific knowledge	Same criteria apply.
4.2 Neurotoxicity	Signs of neurotoxicity after acute or subchronic administration of new compounds in laboratory or target animals may require more detailed studies. • Required if substance belongs to: organophosphates, pyrethroids, carbamates avermectins • Oral route (OECD 424) OPs:delayed neurotoxicity: single dose (OECD 418); repeated dose (OECD 419)	Same criteria apply.
4.3 Microbiological studies 4.3.1 potential effects on the human gut flora 4.3.2 potential effects on the micro-organisms used for industrial food-processing	• Required if residues of anti-microbial compounds (VICH GL36). • Assessment of the effect of antimicrobial substances on dairy starter cultures EMEA/CVMP/276/1999	Same criteria apply.
4.4 Observations in Humans	Observed effects in human therapy medicinal products. All relevant epidemiological, pharmacological, toxicological, and clinical data to be provided.	Same criteria apply.

563

564 **Table 2 Data requirements for safety testing for a marketing authorisation for minor food-**
565 **producing species (where MRLs are established for the active ingredient in a minor**
566 **food-producing species)**

Annex I of Directive 2001/82/EC as amended by 2009/9/EC[4]	Standard data requirements	Minimum dataset for minor food-producing species[5]
PART III.A SAFETY DOCUMENTATION		
III.A.2 Pharmacological studies 2.1 Pharmacodynamics 2.2 Pharmacokinetics	Cross-reference to studies in Part 4 Details of pharmacological studies in laboratory animals and relevant observations in target species. Depending on the application type, the MRL SR/EPMAR may also be submitted.	The MRL SR/EPMAR may be submitted.
III.A.3 Toxicological studies		
3.1 Single dose toxicity	• Normally 2 mammalian species, but 1 can be replaced by target animal species. Normally 2 routes of administration • To reduce animal numbers, alternative validated protocols and internationally recognized protocols will be accepted • Depending on the application type, the MRL SR/EPMAR may also be submitted.	The MRL SR/EPMAR may be submitted if relevant studies are reported.
3.2 Repeat dose toxicity	• 90 day study • 2 species, 1 must be non-rodent • Oral administration • Chronic toxicity study[6]	The MRL SR/EPMAR may be submitted.
3.3 Tolerance in the target species	Cross-reference to studies in Part 4, Chapter I, Section B.	Same criteria apply.
3.4 Reproductive toxicity including teratogenicity		
3.4.1 Study of the effects on reproduction	2-generation study in at least 1 species usually rodent. Depending on the application type, the MRL SR/EPMAR may also be submitted.	The MRL SR/EPMAR may be submitted.
3.4.2 Embryotoxic/fetotoxic effects including teratogenicity	At least 2 mammalian species usually rodent and rabbit	The MRL SR/EPMAR may be submitted.
3.5 Mutagenicity	Testing strategy in accordance with current state of scientific knowledge (VICH GL23R). Depending on the application type, the MRL SR/EPMAR may also be submitted.	The MRL SR/EPMAR may be submitted.

[4] Commission Directive 2009/9/EC amending Annex I to Directive 2001/82/EC
[5] The toxicological data package must allow full assessment of user safety issues and concerns (see CVMP guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-Rev.1))
[6] The VICH GL37 (repeat-dose chronic toxicity testing) indicates that most veterinary drugs will need to be tested for the adverse consequences of chronic exposure, as there is a potential for consumers to be exposed repeatedly throughout their lifetime. However, the guideline does not preclude the possibility of alternative approaches that may offer an equivalent assurance of safety, including scientifically based reasons as to why chronic toxicity testing may not need to be provided.

Annex I of Directive 2001/82/EC as amended by 2009/9/EC[4]	Standard data requirements	Minimum dataset for minor food-producing species[5]
3.6 Carcinogenicity	Long term carcinogenicity study for substances required if: i) have a close chemical analogy with known carcinogens (referred to as "Structural Alerts") ii) positive mutagenicity tests iii) suspect signs during toxicity testing Studies designed in accordance with current state of scientific knowledge Depending on the application type, the MRL SR/EPMAR may also be submitted.	The MRL SR/EPMAR may be submitted.
III.A.4 Studies of Other Effects		
4.1 Special studies	Special studies including specific target organ toxicity (e.g. immunotoxicity, endocrine function tests, liver and renal function tests, effects on enzymes, neurotoxicity, sensitisation, skin and eye irritation, inhalation toxicity, mechanistic studies, relay toxicity studies, etc. as appropriate). Depending on the application type, the MRL SR/EPMAR may also be submitted.	Data not required unless relevant effects in repeat dose studies have been observed. The MRL SR/EPMAR may be submitted.
4.2 Observations in humans	Observed effects in human therapy medicinal products. Depending on the application type, the MRL SR/EPMAR may also be submitted.	The MRL SR/EPMAR may be submitted.
4.3 Microbiological studies	• Required if residues of anti-microbial compounds • Investigate risk to human intestinal flora and risk of resistance development • Investigate if residues can affect processes in industrial foodstuffs processes • Depending on the application type, the MRL SR/EPMAR may also be submitted.	The MRL SR/EPMAR may be submitted.
4.4 Studies on metabolites, impurities, other substances and formulation	Appropriate studies to assess the toxicity of metabolites, impurities, other substances and formulation	Same criteria apply.
III.A.5 User safety	The requirements of the user safety guideline (EMEA/CVMP/543/03-Rev.1) should be applied.	Same criteria apply.
III.A.6 Ecotoxicity	Environmental Risk Assessment (ERA) in accordance with the existing VICH/CVMP (Phase I/II) Guidelines required.	Same criteria apply.

567

568 **Table 3 Data requirements for safety testing for a marketing authorisation for non-food-**
569 **producing species**

Annex I of Directive 2001/82/EC as amended by 2009/9/EC	Standard data requirements	Minimum dataset for minor food-producing species
PART III.A SAFETY DOCUMENTATION		
III.A.2 Pharmacological studies 2.1 Pharmacodynamics 2.2 Pharmacokinetics	Cross-reference to studies in Part 4. Details of pharmacological studies in laboratory animals and relevant observations in target species	Same criteria apply. For well established use applications, the MRL SR/EPMAR may also be used, if available.
III.A.3 Toxicological studies		
3.1 Single dose toxicity	• Normally 2 mammalian species, but 1 can be replaced by target animal species. Normally 2 routes of administration • To reduce animal numbers, alternative validated protocols and internationally recognized protocols will be accepted	Same criteria apply. For well established use applications, the MRL SR/EPMAR may also be used, if available if relevant studies are reported.
3.2 Repeat dose toxicity	Study in 1 species and this may be replaced by the target species; Tests may be modified (with justification) for new combinations of known substances	Same criteria apply. For well established use applications, the MRL SR/EPMAR may also be used, if available.
3.3 Tolerance in the target species	Cross-reference to studies in Part 4, Chapter I, Section B.	Same criteria apply.
3.4 Reproductive toxicity including teratogenicity.		
3.4.1 Study of the effects on reproduction	A study of developmental toxicity in at least one species is required. The species selected may be the target species. Depending on the application type, the MRL SR/EPMAR may also be submitted (if available). (These data are not required for TAS evaluation for non-food producing species unless the product is intended for use in animals which might be used for breeding. For evaluation of TAS these data are not required for topical use products if negligible systemic absorption.) These data will normally be required for evaluation of user safety.	Same criteria apply. For well established use applications, the MRL SR/EPMAR may also be used, if available.
3.4.2 Embryotoxic/fetotoxic effects including teratogenicity	A study of developmental toxicity in at least one species is required. The species selected may be the target species. Depending on the application type, the MRL SR/EPMAR may also be submitted.	Same criteria apply. For well established use applications, the MRL SR/EPMAR may also be used, if available.
3.5 Mutagenicity	Testing strategy in accordance with current state of scientific knowledge (VICH GL23R).	Same criteria apply. For well established use applications, the MRL SR/EPMAR may also be used, if available.
3.6 Carcinogenicity	Long term carcinogenicity study for substances required if: i) have a close chemical analogy with	Same criteria apply. For well established use applications,

Annex I of Directive 2001/82/EC as amended by 2009/9/EC	Standard data requirements	Minimum dataset for minor food-producing species
	known carcinogens (referred to as "Structural Alerts") ii) positive mutagenicity tests iii) suspect signs during toxicity testing Studies designed in accordance with current state of scientific knowledge Depending on the application type, the MRL SR/EPMAR may also be submitted.	the MRL SR/EPMAR may also be used, if available.
III.A.4 Studies of Other Effects		
4.1 Special studies	Special studies including specific target organ toxicity (e.g. immunotoxicity, endocrine function tests, liver and renal function tests, effects on enzymes, neurotoxicity, sensitisation, skin and eye irritation, inhalation toxicity, mechanistic studies, relay toxicity studies, etc. as appropriate). Depending on the application type, the MRL SR/EPMAR may also be submitted.	Data not required unless relevant effects in repeat dose studies have been observed. For well established use applications, the MRL SR/EPMAR may be submitted, if available.
4.2 Observations in humans	Observed effects in human therapy medicinal products. Depending on the application type, the MRL SR/EPMAR may also be submitted.	Same criteria apply. For well established use applications, the MRL SR/EPMAR may be submitted, if available.
4.3 Microbiological studies	Not required.	
4.4 Studies on metabolites, impurities, other substances and formulation	Appropriate studies to assess the toxicity of metabolites, impurities, other substances and formulation	Same criteria apply. For well established use applications, the MRL SR/EPMAR may be submitted, if available.
III.A.5 User safety	The requirements of the user safety guideline (EMEA/CVMP/543/03-Rev.1) should be applied.	Same criteria apply.
III.A.6 Ecotoxicity	Environmental Risk Assessment (ERA) in accordance with the existing VICH/CVMP (Phase I/II) Guidelines required.	Same criteria apply.

570

571 **Table 4 Current data requirements for residues studies for MRL and withdrawal periods**
572 **(see text of document for possibilities for extrapolation)**

	Establishment of MRL		Establishment of withdrawal periods	
	Major Species	**Minor Species**	**Major Species**	**Minor Species**
Meat: Muscle (including injection site), fat (skin+fat for pigs and poultry), liver, kidney. Muscle and skin in natural proportions for fish	Large animals (mammals): 4 animals/time point Poultry: 6 animals/time point Fish: 10 animals/time point (for all species usually 4-5 time points recommended) VICH GL46	1-4 animals in total, 1 time point close to the MRL Extrapolation is also possible. See criteria in the text.	Minimum 4 animals/time point at a minimum of 4 time points as stated in VICH GL48(R) (EMA/CVMP/VICH/ 463199/2009).	No specific conditions for minor species. Under certain conditions, withdrawal periods could be extrapolated from major species. See main text.
Milk	≥8 as in VICH GL46	No specific conditions for minor milk-producing species. Extrapolation is also possible. See criteria in the text.	At least 20 as set out in VICH GL48R	No specific conditions for minor milk-producing species. Under certain conditions, withdrawal periods could be extrapolated from major species. See main text.
Egg	≥10 eggs/day for laying birds over a sufficiently long time period. VICH GL46	No specific conditions for minor eggs-producing species. Extrapolation is also possible. See criteria in the text.	At least 10 eggs as set out in VICH GL48R	No specific conditions for minor milk-producing species. Under certain conditions, withdrawal periods could be extrapolated from major species. See main text.
Honey	At time of publication: 5 samples of each of 5 hives. Note that VICH expected to publish new guidance on residue studies in honey during 2016		At time of publication: 5 samples of each of 5 hives. Note that VICH expected to publish new guidance on residue studies in honey during 2016.	

573

574 **Table 5 Current data requirements for analytical methods**

Routine Analytical Method proposed for residues monitoring		Analytical Method validation for withdrawal period	
Major Species Vol. 8	**Minor Species**	**Major Species**	**Minor Species**
LOD (n > 20 blank samples) LOQ (at least 1/2 MRL) Accuracy: 3 analyte levels (1/2MRL-2xMRL), n=6/level Precision: Repeatability: 3 analyte levels (1/2MRL, MRL, 2xMRL), n=6/level Within Laboratory Reproducibility 3 analyte levels (1/2MRL, MRL, 2xMRL), n=6 at n 3 separate days Specificity against homologues/analogues	Same requirements as for major species, except as follows: Determination of LOQ, accuracy and precision can be combined 5): LOQ: 1/2 MRL Accuracy: 1 analyte level at 1/2 MRL, n=5 at 3 separate days Precision: 1 analyte level at 1/2 MRL, n=5 at 3 separate days Minimum sample requirement 2): 1 blank sample 1 analyte level (at MRL), n=2 Stability: 1 analyte level (n=2)	In principle the same requirements as for routine analytical methods, except for specificity testing. As in VICH GL49.	In principle the same requirements as for routine analytical methods for minor species. As in VICH GL49.

575 # References

576 The following legislation, guidelines and notes for guidance are relevant to this guideline:

577 1. Revised Policy on Classification and Incentives for Veterinary Medicinal Products indicated for Minor
578 use Minor species (MUMS)/limited market
579 (EMA/308411/2014) http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_p
580 rocedural_guideline/2014/09/WC500172928.pdf

581 2. Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the
582 Community code relating to veterinary medicinal
583 products http://ec.europa.eu/health/files/eudralex/vol-5/dir_2001_82/dir_2001_82_en.pdf

584 3. Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 laying
585 down Community procedures for the establishment of residue limits of pharmacologically active
586 substances in foodstuffs of animal origin, repealing Council Regulation (EEC) No 2377/90 and
587 amending Directive 2001/82/EC of the European Parliament and of the Council and Regulation (EC)
588 726/2004 of the European Parliament and of the
589 Council http://ec.europa.eu/health/files/eudralex/vol-5/reg_2009-470/reg_470_2009_en.pdf

590 4. Rules Governing Medicinal Products in the EU: Notice to Applicants and Note for Guidance, Volume
591 8 "Establishment of maximum residue limits of veterinary medicinal products in foodstuffs of
592 animal origin" http://ec.europa.eu/health/documents/eudralex/vol-8/index_en.htm

5. 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:

- 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 resdidues (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 GL6: Ecotoxicity Phase I (CVMP/VICH/592/98-FINAL)
- 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)
- 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 *Salmonidae* and other fin fish (EMEA/CVMP/153b/97-FINAL)
- CVMP guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-Rev.1)
- CVMP Note for guidance on the establishment of maximum residue limits for minor animal species (EMEA/CVMP/153a/97)
- 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).