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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

GUIDELINE ON

SAFETY AND RESIDUE DATA REQUIREMENTS FOR VETERINARY MEDICINAL PRODUCTS INTENDED FOR MINOR USES OR MINOR SPECIES

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GUIDELINE ON SAFETY AND RESIDUES DATA REQUIREMENTS FOR VETERINARY MEDICINAL PRODUCTS INTENDED FOR MINOR USES OR MINOR SPECIES

TABLE OF CONTENTS

1. INTRODUCTION

For some time there has been considerable concern amongst all parties connected with animal health in the EU, especially the veterinary profession, about the decrease in the availability of authorised veterinary medicinal products. This problem is particularly acute in relation to availability of medicines for minor uses and minor species, where there are no authorised products for some uncommonly encountered disease conditions in major species or no authorised products at all for many indications in certain minor species. The EMEA 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 was active in initiatives to address the problem of lack of veterinary medicines.

The CVMP and its Efficacy Working Party (EWP) developed a document called Points to Consider Regarding Efficacy Requirements for Minor Species and Minor Indications (EMEA/CVMP/610/01-Consultation), which was released for public consultation in February 2002. Having reviewed comments received from interested parties following the release of that document, the Committee developed its Position Paper Regarding Availability of Products for Minor Uses and Minor Species (MUMS) (EMEA/CVMP/477/03). That document aims to define the problem in some depth and makes suggestions for possible solutions. The proposals are characterised as short, medium and long-term goals.

One of the main goals for CVMP is to review dossier requirements for veterinary medicinal products intended for minor uses and minor species and, if possible, to establish standards for demonstration of quality, safety and efficacy for these.

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. However, the CVMP is willing to give consideration to the development of specific additional guidance to facilitate the development of specific veterinary medicinal products for minor uses or minor species should proposals for such guidance be deemed necessary.

This guideline supersedes the CVMP Note for Guidance on the Establishment of Maximum Residue Limits for Minor Animal Species, EMEA/CVMP/153a/97.

2. SCOPE

The objectives of this guideline are:

- to provide applicants with information on safety and residues data requirements for the establishment of MRLs for minor species,
- to provide applicants with information on safety and residues data requirements for marketing authorisations of pharmaceutical veterinary medicinal products intended for minor species.

This document addresses the above objectives in 3 sections as follows:

- The general data requirements for minor species for an MRL application.
- The general data requirements for minor species for a Marketing Authorisation application for a food producing species.
- The general data requirements for a minor species for a Marketing Authorisation application for non-food producing species.

2.1 Definitions

Minor Species

There is no legislative definition in the EU for major or minor species. However, major species were defined by the CVMP according to animal population data and total consumption figures, using total numbers across the European Union for the purpose of CVMP guidelines. All other animal species, which are not considered major, are as a consequence, by default, classed as minor (for details see CVMP Position Paper regarding availability of Products for Minor Uses and Minor Species (MUMS), EMEA/CVMP/477/03-FINAL).

Minor Use

There is no legislative definition in the EU of a 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. The minor use of a product will be considered on a case-by-case basis taking into account justification put forward by an Applicant to support the minor use of a product. (see Position Paper regarding availability of Products for Minor Uses and Minor Species (MUMS), EMEA/CVMP/477/03-FINAL). Applicants are advised to seek scientific advice from the CVMP before submitting an application.

3. LEGAL BASIS

Council Regulation (EEC) No 2377/90 of 26 June 1990, as amended, lays down a Community procedure for the establishment of maximum residue limits (MRLs) of veterinary medicinal products in foodstuffs of animal origin (Official Journal L 224 of 18 August 1990). The information required for the establishment of MRLs by the European Union is set out in Annex V of the above-mentioned Regulation, as amended by Commission Regulation (EEC) No 762/92.

Requirements for safety testing for a marketing authorisation application are laid down in Article 12 of European Parliament and Council Directive 2001/82/EC as amended by Directive 2004/28/EC, and are specified in Annex I of Directive 2001/82/EC, as amended. This Annex is currently under revision.

One of the intentions of the revised legislation for the authorisation of veterinary medicines as laid down in the preambles Nr. 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."

4. MRL APPLICATIONS FOR MINOR SPECIES WITH NO MRL ESTABLISHED – GENERAL REQUIREMENTS

4.1 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 exposure (e.g. developmental toxicity, mutagenicity) could not be reduced for minor species.

4.1.1 Establishment of the ADI and MRL in a minor species – Tabulated minimum datasets

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 for the same, where MRLs have not been established for use in a major food-producing species. It should be noted that for the safety evaluation based on a minimum data sets according to this guideline additional uncertainty factors will be used to address the absence of data[1]. It is proposed that based on such a minimum safety data set and applying an appropriate uncertainty factor a temporary ADI[2] can be determined which in turn is the basis of the MRLs to be established for the minor species under consideration.

The safety evaluation according to this guideline will be relevant to minor species only and will not be valid for the establishment of MRLs for a major species, for which a full data package according to Volume 8 of the Rules Governing Medicinal Products in the European Union[3] will be required.

4.1.2. 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 target species, 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. It may be possible to cross-refer to data submitted in the residues dossier, such as the radiolabelled study in the target species (for marker residue to total residue ratio) or the residues depletion study.

4.1.3. Toxicological data

Toxicological data are required for an assessment of adverse affects 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

[1] This uncertainty factor should be sufficiently high so if establishing a final ADI, once additional information is provided, such final ADI would not be lower. It should be noted that there is guidance for default uncertaintly (safety) factors in Volume 8.

[2] Council Regulation 2377/90 Article 1(b), second paragraph, allows for the establishment of temporary ADIs that utilise an additional safety (uncertainty) factor.

[3] Rules Governing Medicinal Products in the EU: Notice to Applicants and Note for Guidance, Volume 8 "Establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin"

conducted in accordance with the relevant OECD guidelines or other internationally recognised guidelines. Any deviation should be adequately justified.

4.2 Residue data requirements

4.2.1 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 marker to total residues, if necessary. Possible exemptions are substances where there is evidence that the residue of concern relates to a single active component only (e.g. pharmacologically or microbiologically active component in case of pharmacological/microbiological ADI). For a novel compound intended for minor species, the radiolabelled study could be dispensed on a case-by-case basis when scientifically justified upon request and supported by substitute data. The CVMP could give scientific advice on this issue to the applicant before the application is submitted to EMEA. 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) 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 marker: 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 requested. Radiolabelled studies are not required to assess an MRL in honey.

4.2.2 Marker residue studies

Where MRLs need to be established in the minor species marker residue studies according to Volume 8 should be submitted.

4.2.3 Regulatory analytical methods

For the purposes of monitoring of residues there is a need for a regulatory analytical method also 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 detection” and 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 stability data should be supplied.

4.3 Extrapolation of MRLs

4.3.1 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 been developed previously (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 guidance as described in the latter document EMEA/CVMP/187/00-FINAL is as follows: In cases where identical or only slightly different MRLs exist in major species 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 considered not necessary that a fully validated method is also provided. It is normally sufficient to demonstrate that the method developed for the major species is basically 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 exposure situation of the consumer 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 guideline on the establishment of MRLs for *Salmonidae* and other finfish, 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.
Analytical methods should be available 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. Analytical methods should be available for monitoring residues in edible tissues and products of all food-producing animals as outlined above.

iv) When extrapolating the MRL to a minor species, if a validated method for major species is available, it is considered not necessary that a fully validated method is also provided for minor species. It may be sufficient to demonstrate that the method developed for the major species is basically applicable in the minor species. Furthermore, when extrapolating the MRL to another species confirmation is asked whether the marker residue does exist in the new species.

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).

4.4 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.

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 decay 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 practise. No MRL can be proposed if this criterion is not met.

5. MARKETING AUTHORISATION APPLICATIONS FOR FOOD PRODUCING SPECIES – GENERAL REQUIREMENTS

5.1 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.

5.1.1 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 major or minor food producing species, in accordance with Part 3A Safety Testing as laid down in Annex I[4] of Directive 2001/82/EC, as amended with the exception of ecotoxicity requirements and in accordance with the CVMP/VICH Safety guidelines.

[4] Details are found in Directive 2001/82/EC, as amended, Annex I, Title I Requirements for Veterinary Medicinal Products other than Immunological Veterinary Medicinal Products, Part 3, Safety and Residues Testing.

5.1.2 Marketing Authorisation applications and the use of MRL Summary Reports in accordance with Directive 2001/82/EC, as amended

It should be noted that Directive 2004/28/EC, as amended, permits Marketing Authorisation applications made in accordance with Article 13a, to submit the published EMEA/CVMP MRL Summary Report 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 Summary Report as part of the published literature submitted.

5.1.3 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 EMEA/CVMP MRL Summary Report.

5.1.4 Toxicological data

Toxicological data are required for the establishment 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.

5.1.5 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-FINAL) 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.

5.1.6 Environmental safety

Ecotoxicity requirements should be addressed by referring to the CVMP/VICH Phase I guidance as given in the guideline on Environmental Impact Assessment (EIAs) for veterinary medicinal products (VMPs) Phase I CVMP/VICH/592/98-FINAL.

5.2 Residue data requirements

5.2.1 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 product 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).

5.2.1.1 Identical products

In case of the same veterinary medicinal product with the same MRL in the major/minor species, it could be considered to follow an approach similar to the approach for extrapolation of MRLs, i.e. no specific or no residue depletion studies 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 intramuscular and subcutaneous injectables and 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).

5.2.1.2 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 injectables 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. 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). This approach, however, could lead to unnecessarily long and impracticable withdrawal periods.

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 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 an abbreviated validation of the analytical method could be acceptable. It could be sufficient to validate the method for accuracy and precision at two concentration levels only – e.g. at the level of the MRL and one half the MRL (see below at 5.2.1.4 and also Table 5).

5.2.1.3 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.

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

The analytical method used in a residue depletion study must be validated to some extent, otherwise the study itself would not be valid. If the analytical method had been used for the residue studies in a major species, then applicants might send an abbreviated set of data.

For the purpose of residue studies in a minor species, a minimum validation of the analytical methods could be acceptable. It could be sufficient to validate the method for accuracy and precision at the level of interest only, e.g., at the level of the MRL and half the MRL if the aim of a study is to demonstrate that residues are below this level, similar to the approach described 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). Adequate storage stability data should be supplied as well when samples are stored prior to analysis.

5.2.2 Withdrawal periods for Annex II compounds

Many compounds included in Annex II 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, Criteria for inclusion of substances into Annex II of Council Regulation [EEC) N° 2377/90]). For Annex II compounds, no MRL is available on which to base the withdrawal period. For many compounds in Annex II 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 and warranted for compounds fulfilling Annex II 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 estimating 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 Annex II compounds with no ADI where an alternative exposure limit may serve as reference point for the withdrawal period.

Withdrawal periods for Annex II compounds may also be extrapolated between major and minor species according to the rules under 5.2.1.1 above.

6. MARKETING AUTHORISATION APPLICATIONS FOR NON-FOOD PRODUCING SPECIES – GENERAL REQUIREMENTS

6.1 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, 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.

6.1.1 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 ecotoxicity 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.

6.1.2 Marketing Authorisation applications and the use of MRL Summary Reports 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 Summary Report 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 Summary Report as part of the published literature submitted. Therefore MRL Summary Reports 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.

6.1.3 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.

6.1.4 Toxicological data

Toxicological data are required for the establishment 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 appropiate, 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.

6.1.5 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-FINAL) 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.

6.1.6 Environmental safety

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

7. 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

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).

Council Reg 2377/90 Annex V reference	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 target species, and if available, human data	Details of pharmacokinetic studies in laboratory animals and target species, and if available, human data Cross reference to residues dossier and radiolabelled study in target species for MR:TR ratio and residues depletion, and if available human data.
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[5] (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. The study required is a 2-generation study[6].
3.4.2 Study of developmental toxicity	Developmental toxicity: tiered approach – VICH GL32.[7] (OECD 414)	Same criteria apply. Developmental toxicity: tiered approach – VICH GL32[7].

[5] 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.

[6] The 2 generation study replaces the 1 generation study on the grounds that often the 1 generation study has insufficient scientific significance.

[7] As given in Volume 8

Council Reg 2377/90 Annex V reference	Standard data requirements (as given in Volume 8 October 2005)	Minimum dataset for minor food-producing species
3.5 Mutagenicity	Testing strategy in accordance with current state of scientific knowledge (VICH GL23) The standard battery consists of the following three tests: i) bacterial gene mutation (OECD 471) ii) chromosome aberration (OECD 476) iii) mammalian gene mutation (OECD473) If positive results *in vitro*, *in vivo* testing is required in at least 2 different somatic tissue sites (OECD 474, 475, 486)	Same criteria apply.
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). • If residues can affect processes in industrial foodstuffs processes. CVMP Note for Guidance EMEA/CVMP/276/99	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.	When observations in human are available, these should be provided

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)

Annex I of Directive 2001/82/EC as amended by 2004/28/EC[8]	**Standard data requirements**	**Minimum dataset for minor food-producing species** [9]
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	Cross-reference to target species pharmacological studies in Part 4 should be included by means of a summary of relevant pharmacodynamic effects and ADME.
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	No single dose studies are required but a summary of any observed adverse effects or toxicity, or absence of effects, seen in the target species studies, should be included. Studies should be submitted where they exist in the study archive or in published literature.

3.2 Repeat dose toxicity	• 90 day study
	  • 2 species, 1 must be non-rodent
	  • Oral administration
	• Chronic toxicity study[10]
		Same criteria apply.
		Not required for topical use if negligible systemic absorption.

3.3 Tolerance in the target species		Cross-reference to studies in Part 4, Chapter I, Section B.
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	Not required for topical use if negligible systemic absorption
3.4.2 Embryotoxic/fetotoxic effects including teratogenicity	At least 2 mammalian species usually rodent and rabbit	Absence of studies could be accepted if a valid scientific justification is presented and there are adequate warnings to compensate for the absence of data. Not required for topical use if negligible systemic absorption.

[8] Currently under revision, amendment to be awaited.

[9] The toxicological data package must allow full assessment of user safety issues and concerns (see CVMP guideline EMEA/CVMP/543/03-FINAL)

[10] 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 2004/28/EC	Standard data requirements	Minimum dataset for minor food producing species
3.5 Mutagenicity	Testing strategy in accordance with current state of scientific knowledge (VICH GL23)	Same criteria apply.
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	Same criteria apply. Not required for topical use if negligible systemic absorption.
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)	Data not required unless relevant effects in repeat dose studies have been observed.
4.2 Observations in humans	Observed effects in human therapy medicinal products	Same criteria apply.
4.3 Microbiological studies	• Required if residues of anti-microbial compounds • If residues can affect processes in industrial foodstuffs processes	Same criteria apply.
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-FINAL) should be applied.	Same criteria apply.
III.A.6 Ecotoxicity		Ecotoxicity requirements should be addressed by referring to the VICH Phase I guidance as given in CVMP/VICH/592/98-FINAL

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

Annex I of Directive 2001/82/EC as amended by 2004/28/EC	Standard data requirements	Minimum dataset for minor non-food-producing species[11]
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	Cross-reference to target species pharmacological studies in Part 4 should be included by means of a summary of relevant pharmacodynamic effects and ADME. Absence of studies in laboratory animals must be justified. Detailed pharmacological studies may be required on a case-by-case basis depending on the substance under consideration.
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	No single dose studies required but a summary of any observed adverse effects or toxicity, or absence of effects, seen in the target species studies, should be included. Studies may be submitted where they exist in the study archive or in published literature.
3.2 Repeat dose toxicity	Study in 1 species and this may be replaced by the target animal study; cross reference to target species tolerance studies in Part 4 should be a summary of any observed adverse effects or toxicity, or absence of effects, seen in the target species studies. Tests may be modified (with justification) for new combinations of known substances Not required for topical use if negligible systemic absorption.	Same criteria apply.
3.3 Tolerance in the target species		Cross-reference to studies in Part 4, Chapter I, Section B.

[11] The toxicological data package must allow full assessment of user safety issues and concerns (guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-FINAL))

Annex I of Directive 2001/82/EC as amended by 2004/28/EC	Standard data requirements	Minimum dataset for non-food producing species
3.4 Reproductive toxicity including teratogenicity. 3.4.1 Study of the effects on reproduction	Not required for non-food producing species unless the product is intended for use in animals which might be used for breeding. It is not required for topical use if negligible systemic absorption.	Not required for non-food-producing species unless the product is intended for use in animals which might be used for breeding. It is not required for topical use if negligible systemic absorption.
3.4.2 Embryotoxic/fetotoxic effects including teratogenicity	Not required for non-food producing species unless the product is intended for use in animals which might be used for breeding. If testing required 1 species which can be the target species if intended for animals for breeding. It is not required for topical use if negligible systemic absorption.	Not required for non-food-producing species unless the product is intended for use in animals which might be used for breeding. If testing required 1 species which can be the target species if intended for animals for breeding. Absence of embryotoxic/fetotoxic/ teratogenic studies could be accepted if a valid justification is presented and there are adequate warnings to compensate for the absence of data. It is not required for topical use if negligible systemic absorption.
3.5 Mutagenicity	Testing strategy in accordance with current state of scientific knowledge (VICH GL23)	Same criteria apply.
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	Same criteria apply. Not required for topical use if negligible systemic absorption
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)	No data required unless relevant effects in repeat dose studies have been observed.
4.2 Observations in Humans	Observed effects in human therapy medicinal products	Same criteria apply.
4.3 Microbiological studies	Not required	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..
III.A.5 User safety	The requirements of the user safety guideline (EMEA/CVMP/543/03-FINAL) should be applied.	Same criteria apply.
III.A.6 Ecotoxicity		Ecotoxicity requirements should be addressed by referring to the VICH Phase I guidance as given in CVMP/VICH/592/98-FINAL.

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

	Establishment of MRL		Establishment of withdrawal periods
	Major Species	**Minor Species**	**Major / 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 3-5 time points recommended) [1)]	1 -4 animals in total, 1 time point close to the MRL [2)]	minimum 3 animals/time point at a minimum of 3 time points. Cannot be reduced on statistical grounds. No specific conditions for minor species[3)]
Milk	8 cows (4 low,4 high yielding)	No specific conditions for minor milk-producing species.	More than or equal to 19 cows (low, high yielding). No specific conditions for minor species. Cannot be reduced on statistical grounds No specific conditions for minor species [4)]
Egg	10 eggs/day for laying birds over a sufficiently long time period*	No specific conditions for minor species.	No specific guidance for withdrawal times for eggs. Recommended: 10 eggs/day. Over a sufficiently long time period* No specific conditions for minor species.
Honey		5 samples of each of 5 hives	No specific guidance for withdrawal times for honey.

*****sampling time needs to take into account physiological egg development

TABLE 5 Current data requirements for analytical methods

	Routine Analytical Method		Analytical Methods for Residue Depletion Studies
	Major Species Vol. 8 [1)]	**Minor Species**	**Major/Minor Species**
Analytical Methods	LOD (n ≥ 20 blank samples) LOQ (at least 1/2 MRL) Accuracy: 3 analyte levels (1/2MRL-2xMRL), n=6/level Precision: <u>Repeatability:</u> 3 analyte levels (1/2MRL, MRL, 2xMRL), n=6/level <u>Within Laboratory Reproducibility</u> 3 analyte levels (1/2MRL, MRL, 2xMRL), n=6 at n ≥ 3 separate days <u>Specificity</u> 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 or MRL Accuracy: 1 analyte level at 1/2 MRL or MRL, n=5 at 3 separate days Precision: 1 analyte level at 1/2 MRL or 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. No specific conditions for minor species defined yet

1) Volume 8: Notice to applicants Veterinary medicinal products: Establishment of maximum residue limits (MRLs) for residues of veterinary products in foodstuffs of animal origin;

2)Note for Guidance on the Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food Animal Origin (EMEA/CVMP/187/00-Final);

3) Note for Guidance: Approach towards harmonisation of withdrawal periods (EMEA/CVMP/036/95);

4) Note for Guidance for the determination of withdrawal periods for milk (EMEA/CVMP/473/98-Final).

5) Note for Guidance on the Establishment of Maximum Residue Limits for Minor Animal Species (EMEA/CVMP/153a/97).

REFERENCES

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

- Directive 2001/82/EC of the European Parliament and of the Council as amended by Directive 2004/28/EC
- Council Regulation (EEC) No 2377/90, laying down a Community procedure for the establishment of Maximum Residue Limits of Veterinary Medicinal products in foodstuffs of animal origin
- Rules Governing Medicinal Products in the EU: Notice to Applicants Veterinary Medicinal Products, Volume 6B "Presentation and Content of the Dossier"
- Rules Governing Medicinal Products in the EU: Notice to Applicants and Note for Guidance, Volume 8 "Establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin"
- CVMP Note for Guidance for the Assessment of the Effect of Antimicrobial Substances on Dairy Starter Cultures (EMEA/CVMP/276/99-FINAL)
- Points to consider regarding efficacy requirements for Minor Species and Minor Indications (EMEA/CVMP/610/01-CONSULTATION)
- CVMP Position Paper regarding availability of Products for Minor Uses and Minor Species (MUMS) (EMEA/CVMP/477/03)
- Guideline on User Safety for Pharmaceutical Veterinary Medicinal Products (EMEA/CVMP/543/03-FINAL)
- OECD Toxicity Testing Guidelines
- VICH Safety Guidelines