The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines Evaluation Unit

EMEA/CVMP/153a/97-**FINAL**

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

NOTE FOR GUIDANCE ON THE ESTABLISHMENT OF MAXIMUM RESIDUE LIMITS FOR MINOR ANIMAL SPECIES

FINAL APPROVAL BY CVMP	12 NOVEMBER 1997
DATE FOR COMING INTO OPERATION	12 NOVEMBER 1997

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1. Introduction

One of the major costs in the establishment of an Maximum Residue Limit (MRL) is that incurred by the production of the safety file for a drug so that an acceptable daily intake (ADI) can be calculated. The production of the residues file which provides data which allows the elaboration of the MRL, taking into account ADI, is also cost intensive, particularly as this is essential for each species, and this may have a significant impact as applicants for MRLs are usually unwilling to invest in work for which there is a poor, or even no financial return. This in turn will inevitably lead to animal welfare problems as there will be an increasing shortage of medicines available for use in the so called minor species.

Since the implementation of Council Regulation (EEC) No. 2377/90 in January 1992, very few MRLs have been allocated for therapeutic substances intended for the minor animal species.

It can be concluded that as it is currently implemented, Regulation No. 2377/90 does not favour the establishment of MRLs for these minor animal species. The guideline EMEA/CVMP/062/95 related to this issue, adopted in June 1995, has not so far improved significantly this situation.

This absence of MRLs for minor animal species raises real problems for an appropriate protection of human health with regard to veterinary drug residues likely to be found in the food commodities derived from these animals. The lack of MRLs prevents the competent authorities from:

- establishing appropriate withdrawal times, the only operational concept which provides the guarantee to the consumer that veterinary drugs are used properly with regard to the veterinary drug residues in food;

- organising the control of veterinary drug residues in food commodities derived from these animals in the framework of national programmes of monitoring and surveillance.

Consequently, there is an urgent need to agree upon a practical procedure in order to protect adequately the public health with regard to these residues. A new approach, based on the concept of risk analysis which associates risk assessment and risk management, would be considered.

2. Definitions

For the purposes of this guideline, major food producing species are defined as follows:

- Cattle and Sheep (meat)
- Cattle (milk)
- Pigs
- Chickens (including eggs)
- *Salmonidae*

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Other food producing species which are not included in this list are considered as minor, such as:

- Other ruminants: minor ruminants (*bovidae* including *caprinae)* and their milk, deer (c*ervidae*) including reindeer
- Sheep milk
- Other avian species and their eggs
- Other fish species
- Other mammalian species (horse/rabbit)

3. Possible extrapolation from major to minor animal food producing species

3.1 General strategy

Pharmacokinetic and toxicokinetic considerations generally indicate that metabolism, excretion and disposition (and hence target tissues and marker residues) could in theory differ from species to species. In practice, MRLs for a particular substance are similar, if not identical across a range, albeit limited number of species.

Where a substance is included in Annex I, II or III to Council Regulation (EEC) No. 2377/90 for a major animal species extrapolations to the corresponding minor animal species can be made as shown in the table below:

Major animal species and their products	Extrapolations to	**Minor animal species and their products**
Cattle and sheep meat	"	other ruminant meat
Cattle milk	"	other ruminant milk
Salmonidae	"	other fin fish
Chicken and eggs	"	other avian species and eggs, including turkeys
Relevant species (e. g. ruminants, pigs)	"	horse/rabbit

3.2 Substances already included in Annex II for a major animal species

The existing MRL entry of a substance in Annex II to Council Regulation (EEC) No. 2377/90 for a major animal species should normally also refer to the corresponding minor animal species with the same restrictions, if applicable.

3.3 Substances already included in Annex I or III for a major animal species

A substance already included in Annex I or III of Council Regulation (EEC) No. 2377/90 for a major animal species could also be included in Annex I or III to the above-mentioned Regulation with similar MRLs for the corresponding minor animal species.

The rationale to support this approach is based on the four following criteria.

3.3.1 The numerical value of MRLs

Taking into consideration the concept of the substitution of the food commodities, which means that when a consumer eats 300 g of meat of an animal species, he does not eat, at the same day, 300 g of meat of another animal species, the MRL value should be the same**.**

In case of some differences in the residue depletion studies and residue distribution in tissues between the major and minor animal species which could impact the length of the withdrawal time, the competent authorities will adopt appropriate decisions for the minor animal species during the marketing approval procedure.

3.3.2 Identification of the marker residue

This is the main issue to be considered for an appropriate extrapolation from the major animal species to the minor one.

It has to be borne in mind that, so far, for all the substances already included in both Annexes I and III, the same marker residue applies to all the tissues of all the different major animal species concerned. Therefore it may be possible to accept the extrapolation of a marker residue established for one major animal species which could also be valid for the corresponding minor animal species.

Nevertheless two questions are to be considered.

I. Does the marker residue, established for the corresponding major animal species, also exist in the minor animal species under consideration and if affirmative, can it be used in practice for the purpose of monitoring programmes of residues ?

In order to address this question the applicant should carry out an appropriate residue depletion study in the minor animal species under consideration. By doing so, the applicant should prove with a properly validated method (see point 3.3.4, validation of analytical methods) that the marker residue, established in the corresponding major animal species

- does exist in the corresponding target tissues (see point 3.3.3, target tissues),
- is present in those target tissues in concentrations high enough for this marker residue to be used for the control of veterinary drug residues in food.

If these two requirements are not met, the applicant would have to carry out additional studies in order to identify an appropriate marker residue.

II. Is the ratio between this marker residue and the total residues which are usually considered for the assessment of the daily residue intake in relation to the ADI likely to be similar in major and minor animal species ?

This second issue should be considered by applying a risk analysis approach.

Considering that

- all the safety factors used in the establishment of the ADI and of the amount of the daily ingested food,
- the conservative procedure used to establish withdrawal times,
- the limited consumption of food commodities derived from minor animal species,

it can be concluded that the uncertainty about this ratio, in the corresponding minor animal species, between the marker residues and the total residues is not likely to raise any problem of public health.

In addition, when the assessment of the studied substance in the corresponding major animal species has led to MRLs which result in a theoretical daily residue ingestion far below the value of the established ADI, there is an additional margin of safety for using the same marker residue in the corresponding minor animal species.

3.3.3 Target tissues

The target tissues of the corresponding major and minor species of food producing animals should be the same.

3.3.4 Validation of the analytical method

It could be possible to consider that validated analytical methods in accordance with Volume VI of the Rules Governing Medicinal Products in the European Community and presented in an internationally recognised format, provided for the control of MRLs established for any major animal food producing species, are also valid for the corresponding minor species of food producing animals if the following test is carried out:

· Determination of the limit of quantification at residues concentrations corresponding to the MRL and half the MRL values, as stated in the Position Paper on Requirements for LOQ/MRL ratio of the Committee for Veterinary Medicinal Products (EMEA/CVMP/274/96-FINAL).

  This determination could be carried out at one concentration, with five replicates, during three following days. Therefore, the statistical analysis will provide the necessary information concerning accuracy, repeatability and reproducibility.

4. Substances intended for use in minor animal species, which are not already assessed for a corresponding major animal species

The following abbreviated data package of tests for assessing the toxicity and establishing the ADI for substances exclusively used in minor animal food producing species should be provided:

· Repeated dose toxicity studies in 2 species at 28 days duration or alternatively in 1 species at 90 days duration;

· Battery of tests for mutagenicity as set out in Volume VI;

· Tests for teratogenicity/embryotoxicity;

· One generation reproduction study;

· Study to establish the oral bioavailability of the drug;

· Study on potential effects on the human gut flora, where relevant;

· When observations in human are available, these should be assessed

and

· Residues and metabolic studies in accordance with the requirements of Volume VI.

In any case, an extension of the MRLs in a minor animal food producing species to a major species will require the provision of full safety data in accordance with Council Regulation (EEC) No 2377/90 and Volume VI requirements.

5. Honey

Honey is a marginal food item and all comments concerning the limited number of MRLs established for minor species of food producing animals apply particularly to honey. Therefore the pragmatic approach outlined below should be taken for establishing MRLs for the limited number of therapeutic substances used in this area:

- The parent compound is considered as the marker residue if the applicant is able to prove with a validated analytical method in accordance with Volume VI and presented in an internationally recognised format that the parent compound can be found in honey after the substance under consideration has been given to bees.

- The numerical value of MRLs is determined from a residues depletion study in order to:

  lead to an acceptable daily ingestion of residues (if any) with regard to the established ADI;
  be consistent with the LOQ of the proposed analytical method.

Considering that:

- If good husbandry practices are observed, the likelihood of detecting residues in honey is limited. Treatment of bees when they are collecting nectar from flowers and depositing it in hives is not recommended in normal apiculture management; such treatment is usually conducted at least two weeks before bees begin collecting nectar. Therefore elimination of drug residues resulting from treatment would have occurred before nectar is deposited to produce honey in the hive.

- Moreover, there are two safety factors which result in decreasing the concentration of residues in honey. Firstly, notwithstanding that treatment of bees at least two weeks before collecting the nectar, as is usually the case, may contaminate the initial amounts of honey produced, the rest of the production is likely to be free of any contamination. An additional safety factor is provided for by the farmer who usually treats the disease at the beginning of the outbreak, so that only a small proportion of the hives have to be treated prior to the spread of the disease to the remaining ones

it can be concluded that this approach is not likely to raise any problem of public health.