The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines and Information Technology

EMEA/CVMP/187/00-FINAL

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

NOTE FOR GUIDANCE ON THE RISK ANALYSIS APPROACH FOR RESIDUES OF VETERINARY MEDICINAL PRODUCTS IN FOOD OF ANIMAL ORIGIN

AGREED BY AD-HOC GROUP ON RISK ASSESSMENT/AVAILABILITY	March 2000
SUBMITTED TO THE CVMP	April 2000
ADOPTION BY CVMP FOR CONSULTATION	17 May 2000
START OF CONSULTATION	18 May 2000
END OF CONSULTATION	1 October 2000
ADOPTION BY CVMP	10 January 2001
DATE OF COMING INTO EFFECT	10 April 2001

Public 7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 47
E-mail: mail@emea.eudra.org http://www.eudra.org/emea.html

1. INTRODUCTION

Veterinary medicinal products used in the treatment of disease in animals whose tissues and/or products are destined for human consumption may give rise to residues of such products or their metabolites in these food-producing animals. In order to ensure consumer safety an assessment of the safety of residues of all pharmacologically active substances contained in veterinary products for food-producing animals in accordance with Council Regulation (EEC) No 2377/90, has to be carried out. Regulation 2377/90 lays down that maximum residue limits (MRLs) be established for all pharmacological active substances, where appropriate.

Substances for which definitive MRLs have been established are included in Annex I of Regulation 2377/90. MRLs can also be classified as provisional with an established expiry date; the substance would then be included in Annex III, if no substantial issues relating to human safety remain to be resolved which require the provision of additional data by the applicant. Only where the applicant has satisfactorily answered all outstanding questions can the substance be included in Annex I. Where an evaluation concludes that it is unnecessary to establish MRLs for the protection of public health, such substances are included in Annex II. A safety and residue evaluation may also result in the conclusion that there is no limit below which residues may be considered safe for the consumer, which results in a recommendation to include a substance in Annex IV of Regulation 2377/90. This means that the substance is totally prohibited from use in veterinary medicinal products for food-producing animals. Another conclusion may be that no recommendation for inclusion in any of the annexes can be made due to the insufficiency of the data provided. The net result in the latter case is the same as inclusion in Annex IV, i.e. no medicinal product for food producing animals containing such a substance can be authorised in the EU. The same also applies for substances, where the applications were withdrawn at any point during the assessment process.

During the period from 1992 to 2000 over 700 “old”, 37 “new” and 55 extensions and modifications of substances have been reviewed by the Committee for Veterinary Medicinal Products (CVMP) and MRLs recommendations for inclusion in Annex, I, II or III were made for 618 substances in total. 84 substances were recommended for inclusion in Annex I of Regulation 2377/90, 506 in Annex II and 32 in Annex III. For 11 substances it was considered that their residues, at whatever limit, in foodstuffs of animal origin constitute a hazard to the health of the consumer, and they have been placed in Annex IV. For 39 substances, the CVMP was unable to make a recommendation for inclusion in any of the annexes and for further 57 substances, the applicants withdrew their applications after the receipt of the list of questions.

Of the 84 substances in Annex I 57 (70%) have MRLs for more than one species, including 10 (14%) designated for all food-producing animals. Only for 18 substances had MRLs been set for minor species, e.g. horse, goat and rabbit and this lack of MRLs and the consequent lack of veterinary medicinal products have been identified as causing problems in the treatment of minor species.

In order to propose MRLs in relation to approximately 700 applications since entry into force of Council Regulation (EEC) 2377/90 8 years ago by the legal deadline of 1 January 2000[1], the CVMP has been committed to applying a consistent risk assessment approach for all such substances following a very similar assessment approach used by international bodies such as Codex Alimentarius and JECFA. Having now completed the considerable task of setting MRLs for "old" substances by the given deadline the CVMP considered this milestone to be an appropriate time to review this risk assessment approach based on the experience gained in the last 8 years and where appropriate to adapt currently accepted procedures. In this review particular attention has been given to the concerns that an insufficient number of medicinal products is available to treat diseases occurring in animals, which is particularly alarming for certain species such as sheep and horses, and especially minor animal species, e.g. goats, rabbits and turkeys. Concerns now exist that due to this major deficiency of authorised medicines, the off-label use of products is increasing, which may well jeopardise effective residue control with serious implications for consumer safety. There is also serious concern within the veterinary profession at the increasing therapeutic void resulting from the loss of essential substances with the attendant risks for animal health and welfare, which may also compromise the safe supply of animal protein for the human food supply.

Account was also taken of existing guidelines previously developed by the CVMP in respect of extrapolations from one species to another, in particular with respect to minor species and fish[2,3]. Account has also been taken of the consumption pattern in the EU where according to statistical data for 1990-1997 beef, poultry and pigmeat represent 94% of the total meat consumption in the EU, while e.g. caprine and ovine meat represents only 2-4% of the consumption of animal meat. However, regionally these figures differ, as in some Member States particularly ovine meat represents a much higher percentage of the animal meat consumption. The consumption of fish in the EU amounts to 25% in comparison to the animal meat consumption. Again here this figure will differ regionally.

To conduct the review of the risk assessment approach for the establishment of MRLs the CVMP set up in 1999 a specialised ad-hoc group. The mandate of the ad-hoc group was to establish a CVMP risk assessment policy guaranteeing consumer safety whilst attempting to reduce unnecessary testing requirements. One advantage would be to enable a more pragmatic approach in securing the provision of medicines for treating animals especially those classed as minor species.

This document reflects the actual status of scientific knowledge. In the light of future experience the CVMP will continue to consider the risk analysis approach and extrapolation of MRLs. The evaluation of applications for MRL purposes is being done on substances in use in veterinary medicinal products. Any misuse or illegal use of a substance is not part of the risk analysis described here.

This Note for Guidance will present:

- The current approach and a review of existing assessments
- The future approach for assessments in light of experience

[1] In accordance with Article 14 of Council Regulation (EEC) No 2377/90, as amended by Council Regulation (EC) No 434/97

[2] CVMP Note for Guidance on the establishment of maximum residue limits for minor animal species (EMEA/CVMP/153a/97-FINAL)

[3] CVMP Note for Guidance on the establishment of maximum residue limits in Salmonidae and other fin fish (EMEA/CVMP/153b/97-FINAL)

2. ASSESSMENT OF SAFETY OF RESIDUES: CURRENT APPROACH AND REVIEW OF EXISTING ASSESSMENTS

The evaluation of safety of residues and the consequent establishment of MRLs in accordance with Regulation 2377/90 follow the concept of the risk analysis including risk assessment, risk management and risk communication.

2.1. General risk analysis approach and its interpretation in respect to safety of residues

2.1.1 Risk assessment

Risk assessment is a science-based process involving the four stages:

- Hazard identification
- Hazard characterisation
- Exposure assessment
- Risk characterisation

The purpose is the evaluation of the known or potential adverse effects on health from exposure to food-borne hazards, in this case human exposure to veterinary drug residues.

The purpose of the **hazard identification** is the identification of those drug residues capable of causing adverse effects on health and potentially present in a selected food derived from animals. In the **hazard characterisation** stage the nature of the adverse effects associated with the veterinary residues that may be present in food is evaluated qualitatively and/or quantitatively on the basis of the toxicological and pharmacological studies in laboratory animal species. Where available, observations in humans are considered. At this stage the acceptable daily intake (ADI) is established. The **exposure assessment** refers to the qualitative and quantitative evaluation of the likely intake of drug residues through food of animal origin, i.e. the estimate of the consumer intake. For exposure assessment the identification of a suitable marker residue is important, as well as its relation to the total relevant residue. In the **risk characterisation** a qualitative and/or quantitative estimate is made of the risks to the consumer from residues possibly present in animal products, given the uncertainties of assessment of the probability of occurrence and severity of known or potential adverse health effects in a given population based on hazard identification, hazard characterisation and exposure assessment. The consideration of the risk characterisation will lead to the conclusions, whether MRLs need to be established or not.

2.1.2. Risk management

Risk management is understood as the process of weighing policy alternatives and other factors, and where required, selecting and implementing appropriate prevention and control options including regulation measures.

The most prominent actions included in this step are the inclusion of a substance in Annex I, Annex II, Annex III or Annex IV of Council Regulation 2377/90 and the setting of MRLs, the subsequent establishment of withdrawal periods, as well as the surveillance of residues in accordance with Council Directive 96/23/EEC, for which validated analytical methods must be provided within the MRL procedure.

2.1.3. Risk communication

Risk communication is the exchange of information and opinions concerning risk and risk-related factors among risk assessors, risk managers, consumers and other interested parties. Besides an extensive information exchange during the assessment process between all parties involved in the procedure, the publication of the Summary Reports on the assessment of the individual substances by the EMEA, and publishing of the results of residue surveillance by the competent national authorities is particularly relevant here in complying with the needs of effective risk communication.

2.2. Specific risk analysis approach in relation to safety of residues

As stated above, when carrying out the assessment of safety of residues and establishing MRLs in accordance with Council Regulation 2377/90 the general principles of a risk analysis are applied as defined earlier.

The approach used by the CVMP for the evaluation of the safety of residues is based on the determination of the Acceptable Daily Intake (ADI) on which MRLs are subsequently based. The ADI is an estimate of the residue, that can be ingested daily over a lifetime without a health risk to the consumer. The ADI may be set on the basis of toxicological, pharmacological or microbiological data: whichever is the lowest. When the ADI is based on toxicological or pharmacological data, the lowest no-observable-effect-level (NOEL) with respect to the most sensitive parameter in the most sensitive test species is identified from a battery of toxicology/pharmacology studies, or in some cases, where such data are available, from observations in humans. Often a safety factor of 100 (10 x 10, to correct for intraspecies variability and interspecies extrapolation) is applied to extrapolate from the NOEL to the ADI, but depending on the relevance and the quality of the available toxicity/pharmacology data, safety factors can range from 10 to 1000. For most antimicrobial substances a microbiological ADI is calculated on the basis of sensitivity testing of the relevant micro-organisms of the human gut flora. A number of safety factors is included in the formula used to calculate microbiological ADIs on the basis of *in vitro* data. If such effects are investigated in an *in vivo* model, calculation of the microbiological ADI implies the use of safety factors in the same way as for the toxicological ADI. The substantial safety margin used to calculate the ADI is considered necessary to cover the substantial uncertainties in the models used and their relevance to a diverse population of consumers.

The relevant residues and in particular the marker residue are identified on the basis of pharmacokinetic and depletion studies.

Consideration is also given to the potential consumer intake of residues by calculating the levels of consumption of residues in foods of animal origin on the basis of arbitrarily high fixed consumption values to ensure the protection of the majority of consumers. The daily food basket used for such consumption calculation is comprised of: 0.500 kg of meat[4] or 0.300 kg of fish plus 1.500 kg milk plus 0.100 kg eggs plus 0.020 kg honey. The estimation of the consumer intake also takes into account the residue concentration in the food commodities derived from the pattern of residue depletion of the substance in the target animal. Where appropriate residues from the pesticide use of a substance are also taken into account.

In summary the determination of MRLs is based on the ADI, the identified marker residue and total residues, the EU food basket and the tissue distribution. MRLs are established in such a way that the maximum theoretical intake, as calculated from MRLs and food basket does not exceed the ADI.

[4] 0.500 kg comprises for mammals 0.300 kg of muscle, 0.100 kg of liver, 0.050 kg of kidney and 0.050 kg of fat (for pigs, fat and skin in natural proportions) and for poultry 0.300 kg of muscle, 0.100 kg of liver, 0.010 kg of kidney and 0.090 kg of fat and skin in natural proportions

Once MRLs have been allocated, it is then necessary in the context of granting a marketing authorisation to determine a withdrawal period for such veterinary medicines; this ensures that residues from the product concerned will not exceed the MRLs.

The risk assessment would lead to the inclusion of a substance in Annex II without establishing a maximum residue limit where, considering the hazard characterisation and particularly the exposure assessment it can be concluded that the consumer is not at risk if no MRLs are fixed. Examples would be that the use of a substance would be limited, e.g. only for topical use or only in animals which are unlikely to be slaughtered shortly after the administration of that substance. Also where residues would represent only a small proportion of the ADI the establishment of maximum residue limits may not be necessary. For detailed criteria for the inclusion of a substance in Annex II of Council Regulation (EEC) No 2377/90, see Appendix 1.

2.3. Outcome of the review on existing assessments

2.3.1. Choice of marker residue

Pharmacokinetic and residue depletion studies used for the identification of relevant residues and the marker residue must be provided for all major animal species. In the guidelines on the establishment of MRLs for minor species and *Salmonidae* and other fin fish the CVMP has already recognised that normally the same marker residues apply for all major species and target tissues. Therefore, provisions were made in these guidelines that where MRLs have already been set in a major species, any extrapolation to minor species would not require the full data package for the identification of the marker residues.

An updated and in-depth review of the situation has now been undertaken. It showed that up to now, in the majority of substances for edible tissues (i.e. muscle, liver, fat or fat + skin, and kidney) the same marker residue has been identified for the different target species with the exception of very few cases (number of cases: 5 = 5%). The substances concerned are spiramycin (different marker residue in bovine and chicken in comparison to porcine due to the improved analytical method for porcine), and some antibiotics, where the marker residue has been expressed "as the sum of the antimicrobiologically active substances expressed as parent compound" for one species (josamycine - porcine) and differently for chickens (only the parent compound). For food products, i.e. eggs and milk as opposed to tissues derived from animals (meat), the marker residue was in three cases (flubendazole (in eggs), tiamulin (in eggs) and flunixin (in milk)) different from that retained for the edible tissues.

From this analysis, it can be deduced that the marker residue in the great majority of cases does not vary between species.

For the animal products (eggs, milk and honey), differences may occur. However, specific data are in any case requested and the marker residue is not a limiting factor in extrapolating data from one species to another.

2.3.2 Between species variation of MRLs

The CVMP has addressed itself to the pivotal question as to whether it is necessary that species-specific MRL values are set or whether the same MRLs could be established for all animal species.

For the first substances (penicillins, sulfonamides, tetracyclines) assessed by CVMP in accordance with Regulation 2377/90, MRLs were established without species differentiation and the MRLs were set for all food producing species, without requiring species specific pharmacokinetic and residue data. Codex Alimentarius also previously applied this approach.

More recently data requirements have been increased and Codex Alimentarius and CVMP have both requested species-specific data. With the improvement in the quality of the scientific data made available, specific ratios of marker to total residues have been established for the different target

species so that it has been possible to propose specific MRLs for specific target species and to calculate the total amount of residue likely to be ingested.

In respect to minor species the CVMP already previously explored the possibility and agreed to extrapolate within species families from a major species to a minor species. The CVMP laid down in its Note for Guidance on the establishment of maximum residue limits for minor animal species that a substance already included in Annex I or Annex III of Regulation 2377/90 for a major animal species could be included in Annex I or III of the Regulation with similar MRLs for the corresponding minor animal species in the same class, e.g. ruminants. Also the existing entry of a substance in Annex II for a major species should normally also refer to the corresponding minor species. Only a reduced data package in respect to residue data and analytical methods is then requested to establish MRLs for a minor species, thus greatly facilitating provision of medicines for such species without compromising consumer safety.

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

In the Note for Guidance on the establishment of maximum residue limits for *Salmonidae* and other fin fish the CVMP allowed also for the extrapolation of MRLs to *Salmonidae* and other fin fish, where an MRL had been established for a substance in muscle in a major mammalian species and where certain data to support such extrapolation are provided.

An examination of all MRLs established up to now showed that the vast majority of the substances in Annex I (71%) have the same MRLs for different target species. Species-specific MRLs have been set for 17 substances. In these cases with the exception of 4 substances the range of the variation of the MRLs between species was a factor of two or less. The exceptions were for baquiloprim, sarafloxacin, tilmicosin and ivermectin where the between-species range was up to a factor of 7. From examining all these exemptions in detail it appears that most of the differences can be explained by variations in ratios of the marker residue to total residues. This reflects a variation in metabolic capacity between species rather than a variation in tissue distribution of the parent compound and or relevant metabolites. It must be noted, however, that often the experiments, from which the ratio of the marker residue to total residue are derived, are done with a limited number of animals and, therefore, divergence of these ratios due to relatively large experimental errors often cannot be excluded. In reviewing the impact of harmonising MRLs in the cases, where different values had been set for different species, the recalculation of the total amount of residues likely to be ingested revealed that in all cases except one (rafoxanide) it would be possible to set identical MRLs for the different species without exceeding the ADI

In this context it should be noted that the pharmacokinetic parameters of active substances used in veterinary medicine vary within the same species. The factors influencing such intra-species variation include age of the animal, the breed, the physiological status, the weight, the disease status of the animal as well as the dose form and route of administration used.

In respect to the exposure assessment it should be noted that when estimating the consumption intake for the substances for which MRLs have been set for different species, the calculation must only consider the intake of meat and offal (muscle, fat, liver, kidney) from the species for which the highest consumption figure for the intake of residues would result, as the consumer would not eat e.g. 500 g beef and in addition 500 g sheep meat at the same day.

On completion of a detailed assessment of exposure, taking into particular account the concept of substitution of the food commodities and the results of the analysis of the impact of species differences in MRLs as described above, the Committee concluded that specific MRLs for specific target species may not be necessary to ensure the protection of the health of the consumer, against possible harmful effects resulting from ingestion of residues.

2.3.3 Target tissues

Volume VI (future Volume 8) of the Rules Governing Medicinal Products in the European Community states that *the target tissue is usually, but not necessarily, the tissue with the slowest depletion rate of the residues. When a compound is to be used in lactating animals or laying birds, milk or eggs are target tissues in addition to the target tissue selected for residue-monitoring in the edible carcass.*

An important function of the MRL system is that a withdrawal period can be established, which will ensure that that foodstuffs from animal origin are safe to be eaten; the MRL surveillance programme supports this scheme by controlling the compliance with these requirements. MRL monitoring can only ever be undertaken in a few tissues of a minority of animals. Based on this presumption, the true intent of the legislation can be effected by monitoring one or two target tissues, as by definition, compliance with the MRL for the tissue with the slowest depletion characteristics will automatically imply that other tissues have lower residue concentrations. Therefore, on scientific reasons it is considered sufficient that MRLs for surveillance purposes would be necessary to be set for 2 target tissues only (1 carcass tissue, 1 offal tissue), including the provision of a routine analytical method.

However, having noted the need of reference laboratories for MRLs for all target tissues particularly in respect to the surveillance of imports from third countries, it was concluded that the current scheme of establishing normally MRLs in four target tissues in the edible carcass (muscle, fat (or skin and fat in natural proportions), liver and kidney) be maintained. When a compound is to be used in lactating animals or laying birds, milk or eggs are target tissues in addition to the target tissues selected for residue-monitoring in the edible carcass.

3. APPROACH FOR FUTURE ASSESSMENTS IN LIGHT OF EXPERIENCE

Irrespective of the species to which the active substance is administered, there is substantial agreement that the MRL should, where possible, be the same in each species as the hazard characterisation of the residue is essentially similar and several safety factors have been used in its derivation. Considering the knowledge on the variation of residue depletion within classes of animals and therefore on the exposure assessment the risk characterisation should also not differ substantially within an animal class. Therefore, an extrapolation of MRLs from one species to further species within a class of animals will be considered as the default approach.

Where identical or similar MRLs (i.e. MRL values normally in the same order of magnitude) have been set for three major species from different animal classes (i.e. ruminants (e.g. cattle and sheep), monogastrics (e.g. pigs) and poultry (e.g. chickens), 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 ergo the risk characterisation on the basis of same/similar MRLs for further species beyond the animal classes concerned would be similar.

For minor species, in respect of risk characterisation, any limitations due to the lack of species specific data will be compensated by the fact that the exposure of the consumer to residues in minor species is in general limited.

In this context, it should be understood that the substances used should be authorised in accordance with Council Directive 81/851/EEC and therefore administered in accordance with the directions given on the product labelling. The authorised use of veterinary medicines is the subject of national control measures in Member States and records of such use can be confirmed.

While the establishment of MRLs for major species (i.e. cattle, sheep, pigs, chicken and salmon) is understood as requiring the provision of an analytical method, the availability of analytical methods for use with minor species is not necessary from a risk assessment viewpoint if the normal legal controls are observed. However, it is acknowledged that for the purposes of monitoring of residues for intra-community trade and imports from third countries as well as for transparency purposes, there is a need to have analytical methods in place also for use with minor species. Where 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, for instance by using this method in a confirmatory depletion experiment. Alternatively, a limited number of target tissue samples should be reported (one blank sample, duplicate samples fortified at the level of the MRL directly before analysing, and fortified duplicate samples analysed after a certain time of equilibration). Furthermore, when extrapolating the MRL to another species confirmation is asked whether the marker residue does exist in the new species. Therefore, a depletion experiment with one to four animals and a sampling time, where the tissue concentrations are predicted to be close to the MRLs, is required.

For the assessment of the safety of residues and the establishment of MRLs the following approach should be applied:

1. The essential basis for the establishment of MRLs is the ADI derived from safety data for the substance under consideration.

2. The extrapolation of existing MRLs to other species, which is already foreseen for minor animal species and for Salmonidae and other fin fish as described in the CVMP guidelines mentioned above on this subject can, in the light of the experience gained, be expanded as defined below.

   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	All ruminants
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 fin fish, which already allows an extrapolation from MRLs in muscle of a major species to *Salmonidae* and other fin fish provided that the parent compound is acceptable as marker residue for the MRL in muscle and skin, MRLs can be extrapolated to all food-producing animals. Adequate routine 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 set in cattle (or sheep), pigs and chickens (or poultry), which were however slightly different among species, extrapolation to further species as outlined under ii) would be possible as well. 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. Adequate routine analytical methods should be available for monitoring residues in edible tissues and products of all food-producing animals as outlined above.

3. For major species, as before, in all cases a full package of residue data in all relevant tissues should be provided in order to determine a complete set of MRLs, which is considered necessary to set adequate withdrawal periods as well as for surveillance purposes. Thus MRLs should be set for all relevant tissues, normally four target tissues in the edible carcass (muscle, fat (or skin and fat in natural proportions), liver and kidney) and milk or eggs, where relevant.

The approach outlined above will, without compromising the safety of the consumer,

- encourage the development of drugs to cover minor food-producing animals and thereby diminishing the risk to public health from off-label use of drugs;
- reduce the development costs of new drugs without changing the existing high safety margins for public health.

Appendix 1

Criteria for inclusion of substances into Annex II of Council Regulation (EEC) N° 2377/90 and extension of Annex II classification to other species

Criteria for inclusion into Annex II

1. Article 3 of Council Regulation (EEC) N°2377/90 takes provision for the entry of substances into Annex II if "it appears that it is not necessary for the protection of human health to establish a maximum residues limit".

2. Substances complying with the following criteria are candidates for Annex II:

   - substance is of endogenous origin
   - substance is a normal component of the diet in humans
   - substance is generally recognised as safe for humans

3. Substances complying with the following criteria may be entered into Annex II :

   - use in a small number of individual animals, infrequent or non-regular treatments
   - the animal in unlikely to be sent for slaughter immediately after treatment

4. Substances complying with the following criteria will be assessed on their own merits to see whether they could be entered into Annex II :

   - poor or absent absorption of the gastro-intestinal tract or from sites of local application (e.g. skin or eyes)
   - the substance is rapidly and extensively detoxified or excreted.

Extension of Annex II entry to all food producing species

5. Substances having a species specific pattern of use are not eligible to this extension.

6. Substances referred to in alinea 2 should be given an "all food producing species" designation in Annex II citation, regardless of the species requested by the drug sponsor.

7. Substances referred to in alinea 3 may be given an "all food producing species" designation in Annex II citation.

8. For substances referred to in alinea 4, species specific data may be required to make the necessary judgements and so information may be required for each species concerned before Annex II entry can be contemplated. Such drugs may not be suitable for an "all food producing species" designation.