The rules governing medicinal products
in the European Union **October 2005**

Volume 8

Notice to applicants and

Guideline

Veterinary medicinal products

Establishment of maximum residue limits (MRLs) for residues of veterinary medicinal products in foodstuffs of animal origin

FOREWORD

This Notice to Applicants and Guideline (Volume 8 in the series "Rules governing medicinal products in the European Union") has been prepared by the European Commission services in consultation with the European Medicines Agency (EMEA). This document has no legal force and does not necessarily represent the final views of the Commission. In the case of doubt, reference should be made to the appropriate Community Directives and Regulations.

The document is prepared in accordance with Articles 6 and 7 of Regulation (EEC) No 2377/90[1] as amended. It is important when reading this text to appreciate that the legal requirements of the Regulation must be met and that this document presents the harmonised views of the Committee for Medicinal Products for Veterinary Use (CVMP) of the EMEA on how those requirements may be met.

The document shall provide guidance on the establishment of maximum residue limits (MRLs) for residues of veterinary medicinal products in foodstuffs of animal origin.

The document introduces the legislative basis for the establishment of MRLs and the objective of a safety and residue evaluation in respect to veterinary medicinal products for use in food-producing animals. It provides information on the operational procedure for applications for the establishment of MRLs, provides guidance on the presentation and content of the application dossier. It also provides information on how the safety and residue data are evaluated and describes the assessment approach by the CVMP.

This document has been updated during 2004 to take account of the harmonised data requirements agreed at the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products (VICH) and other agreed guidance and to make it available in one comprehensive document.

This document replaces the version of Volume 8 dated June 2003.

[1] OJ L 224, 18.8.1990. p. 1., as amended by Regulation (EC) 1308/1999, OJ L 156, 23.6.1999, p. 1.

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PART I - Introduction

1. General Introduction

The basic rules governing the marketing of veterinary medicinal products within the European Union is contained in the codified Directive adopted by the European Parliament and the Council in 2001, Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products[2], as amended by Directive 2004/28/EC[3]. Furthermore, Regulation (EC) No 726/2004[4] that repealed Regulation (EEC) No 2309/93[5] lays down a Community procedure for the authorisation and supervision of medicinal products for human and veterinary use and establishes a European Medicines Agency.

Volume 5 of the series entitled "The rules governing medicinal products in the European Union" compiles the legal provisions relating to the authorisation of veterinary medicinal products, while Volumes 6A and 6B give further guidance on their application.

In order to protect the health of the consumer of foodstuffs of animal origin, one of the most important principles laid down in the legislation is that foodstuffs obtained from animals treated with veterinary medicinal products must not contain residues of the medicine or its metabolites which might constitute a health hazard for the consumer. In order to facilitate the uniform application of this principle throughout the European Union, and in order to ensure that differences in the assessment of the effects of residues by Member States do not create barriers to the free movement of foodstuffs of animal origin, on 26 June 1990 the Council adopted Regulation (EEC) No 2377/90 laying down a Community procedure for the establishment of maximum residue limits (MRLs) for veterinary medicinal products in foodstuffs of animal origin. This Regulation has subsequently been amended to introduce values of maximum residue limits for substances used in veterinary medicinal products in the annexes to the Regulation and to adapt the legislation to technical progress and amendments to the regulatory procedures.

The entry into force of this Regulation, on 1 January 1992, had legal consequences from the point of view of marketing authorisation holders for veterinary medicinal products in the European Community. In the Regulation 2377/90 a transition period was granted for the so-called old substances, during which the European Union had to evaluate the substances upon receipt of an MRL application. This transition period, which originally lasted until 1 January 1997, was extended until 31 December 1999 by Regulation (EEC) No 434/97[6] for all "defended" old substances, with the exception of some old substances specified in the legislation (end of transition period for these 1 January 1998). Since 1 January 2000, it is no longer

[2] OJ L 311, 28.11.2001, p. 1.
[3] OJ L 136, 30.4.2004, p. 58.
[4] OJ L 136, 30.4.2004, p. 1.
[5] OJ L 214, 24.8.1993, p.1.
[6] OJ L 67, 7.3.1997, p.1.

possible to use any pharmacologically active substance in veterinary medicinal products for food-producing animals unless the substance concerned has been included in Annex I, II, or III of the Regulation.

With the adoption of Regulation (EC) No 1308/99 the legislation made the European Medicines Agency for the Evaluation of Medical Products (EMEA), established in 1995, responsible for the procedure to process applications for establishment of maximum residue limits. The Agency (renamed the European Medicines Agency in 2004) is responsible for co-ordinating the existing scientific resources put at its disposal by the competent authorities of the Member States for the evaluation and supervision of medicinal products. The Agency delivers scientific opinions on applications for centralised marketing authorisation for both human and veterinary use as well as the establishment of MRLs. The Agency comprises the Committee for Medicinal Products for Human Use (CHMP), the Committee for Medicinal Products for Veterinary Use (CVMP), the Committee on Orphan Medicinal Products (COMP), the Committee on Herbal Medicinal Products (HCMP) and a Secretariat providing technical, scientific and administrative support and ensuring appropriate co-ordination. The CVMP is responsible for preparing the opinion of the Agency on any question relating to evaluation of veterinary medicinal products and the establishment of MRLs for veterinary medicinal products in foodstuffs of animal origin.

2. General principles of the safety evaluation of residues of veterinary medicinal products in the European Union

In Regulation (EEC) No 2377/90, a maximum residue limit (MRL) is defined as:

"The maximum concentration of residue resulting from the use of a veterinary medicinal product (expressed in mg/kg or μg/kg on a fresh weight basis) which may be accepted by the Union to be legally permitted or recognised as acceptable in or on a food".

It should be noted that this definition is virtually the same as that adopted by the FAO/WHO Codex Alimentarius Committee for Residues of Veterinary Drugs in Foods. Indeed, the overall approach to the safety evaluation of residues of veterinary medicinal products within the European Union is similar to that employed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) which undertakes the safety evaluation of residues of veterinary medicines for Codex Alimentarius.

The approach used by the CVMP for the evaluation of the safety of residues is similar to the approach used by other committees and international scientific bodies charged with the safety evaluation of food additives and contaminants, based on the determination of a no/lowest-effect-level and the use of uncertainty factors to determine an acceptable daily intake (ADI) on which subsequently MRLs are based.

Nevertheless, there are certain specific differences between the evaluation of the safety of residues of veterinary medicines and the evaluation of other residues such as of food additives or contaminants.

First, because of the properties of the active substances used in veterinary medicine, account must be taken not only of the toxicological properties of the substances in the limited sense of the term (such as

teratogenic, mutagenic or carcinogenic effects) but also of their pharmacological properties. Moreover, in the case of antibiotics and similar substances, the possibility of a microbiological risk addressing both the development of antimicrobial resistance in bacteria of the human gut flora and disruption of the colonisation barrier may also need to be considered.

Secondly, account must be taken of the fact that the residues to which the consumer of foodstuffs of animal origin are exposed may not necessarily be the same as the parent drug substance, since the original substance may be extensively metabolised within the treated animal.

Following the completion of the various pharmacological, toxicological, microbiological and other tests undertaken to demonstrate the safety of the substance, the first major stage in the process of safety evaluation is the establishment of the acceptable daily intake (ADI). The ADI is an estimate of the substance and/or its residues, expressed in terms of μg or mg per kg bodyweight, that can be ingested daily over a lifetime without any appreciable health risk to exposed individuals.

The basis for the calculation of the ADI is the no observed (adverse) effect level (NO(A)EL) or, in certain cases the lowest observed (adverse) effect level (LO(A)EL)[7] with respect to the most sensitive parameter in the most sensitive appropriate test species, or in some cases, in humans. An uncertainty factor (UF) [often called a safety factor] is then applied to take into account the inherent uncertainties in extrapolating animal toxicity data to human beings and to take account of variations within the human species[8]. The ADI concept is not applicable to substances for which it is not possible to determine a NOEL because they demonstrate non-threshold effects (such as genotoxicity and delayed neurotoxicity). In such cases, an alternative approach to safety evaluation may be applied on a case by case basis, having regard to all the data available.

Once the ADI has been agreed, it is then necessary to determine MRLs for the individual food commodities concerned. Since the ADI is related to body weight, an arbitrary average human bodyweight is defined at 60 kg – this is considered to be an average value for all age groups in the European population. The ADI expressed on a μg or mg per kg body weight basis is therefore multiplied by 60 to give the total amount of residue, which can be ingested by an individual.

Moreover, consideration also has to be given to the levels of consumption of foods of animal origin. Since accurate consumption figures are difficult to obtain, and there are substantial variations between individual consumers and between groups of consumers, arbitrarily high fixed values are used to ensure the protection of the majority of consumers.

Thus, in order to derive MRLs from the ADI it is assumed that the average person consumes, on a daily basis, 500 g of meat (made up of 300 g of muscle, 100 g of liver, 50 g of kidney and 50 g of fat) together

[7] For brevity the term NOEL is used generically in the remainder of this document, except where reference is made to a specific effect level.

[8] See Part III. A. II. 5.1 for details

with 1.5 litres of milk and 100 g of eggs or egg products. Allowance is also made for the consumption of poultry, fish and honey (see page 58 of this volume). The total amount of residues present in this daily food basket is not allowed to exceed the ADI.

MRLs are then allocated to the individual food commodities concerned: muscle tissue, liver, kidney, skin and fat, eggs, milk and honey. At this stage, account is also taken of the pattern of residue depletion of the substance through the target animal, and the possible persistence of residues in specific organs such as the liver or kidneys. The MRLs allocated to animal tissues apply to the species indicated in the annexes of Regulation No (EEC) 2377/90.

Regulation (EEC) No 2377/90 recognises that in certain instances it may not be necessary, with respect to public health, to establish MRLs for a particular substance. Such substances are to be included in Annex II of the Regulation. However, substances may only be listed in Annex II after a comprehensive safety and residue evaluation of the substance concerned.

Once MRLs have been allocated, it is necessary in the context of granting marketing authorisations for veterinary medicinal products to determine withdrawal periods. The withdrawal period is the time after the last administration of the veterinary medicinal product during which the animal must not be slaughtered or during which milk or eggs must not be taken for human consumption, ensuring that residues will not exceed the MRLs. Since the withdrawal period will depend on the individual pharmaceutical formulation concerned, specific withdrawal periods will be determined as part of the process of evaluation of the application for marketing authorisation. Thus, depending on the procedure chosen by the applicant to obtain a marketing authorisation, withdrawal periods will either continue to be determined by Member States, where the product is authorised via the mutual recognition or national procedure, or for marketing authorisation procedures through the central route, it will be proposed by the CVMP. In order to ensure a uniform approach to the establishment of withdrawal periods throughout the European Union, the CVMP has drawn up a Note for Guidance regarding withdrawal periods for animal tissues (EMEA/CVMP/036/95) and milk (EMEA/CVMP/473/98). The current Guidelines established by the CVMP (and application software) can be obtained from the EMEA website at http://www.emea.eu.int and are listed in Annex I of this document.

PART II Notice to applicants for the establishment of maximum residue limits (MRLs) for residues of veterinary medicinal products in foodstuffs of animal origin by the European Union in accordance with Regulation (EEC) No 2377/90

I. Purpose and scope of Regulation (EEC) No 2377/90

1. The objectives of Regulation (EEC) No 2377/90

The use of veterinary medicinal products in food-producing animals may result in the presence of residues in foodstuffs of animal origin.

Historically, in many Member States, the control of residues was based upon the concept of zero residue tolerance. Withdrawal periods were calculated so that no residue could be detected using the available analytical methods. However, following developments in analytical methodology, it became possible to detect residues at ever-lower levels. With the adoption of Regulation (EEC) No 2377/90, the Council provided for the establishment of maximum residue limits (MRLs) for residues of pharmacologically active substances which are used in veterinary medicinal products in respect of all the various foodstuffs of animal origin including meat of mammals, poultry, fish, milk, eggs or honey. These MRLs are based on the evaluation of consumer safety rather than developments in analytical methodology.

The primary purpose of establishing MRLs is to ensure the protection of the consumer against possible harmful effects resulting from exposure to residues. Thus MRLs are to be established in accordance with general principles of safety assessment. The principles to be applied to the safety assessment of residues of veterinary medicinal products are described in detail in this guideline on the application of Annex V of Regulation (EEC) No 2377/90 with a view to the demonstration of the safety of a veterinary medicinal product. This guideline is reproduced in Part III of the present volume.

However, as the preamble to Regulation (EEC) No 2377/90 recognises, the establishment of MRLs may also further a number of other objectives, in particular it should facilitate the marketing and free trade within the European Union of foodstuffs of animal origin.

2. Scope of Regulation (EEC) No 2377/90

In accordance with Article 1 (1) (a) of Regulation (EEC) No 2377/90, as amended, residues of veterinary medicinal products means all pharmacologically active substances, whether active principles, excipients or degradation products, and their metabolites which may remain in foodstuffs obtained from animals to which the veterinary medicinal product in question has been administered.

It follows from this definition that MRLs will need to be established not only in respect of the active substances used in veterinary medicinal products, but also in respect of excipients which are capable of having a pharmacological effect.

In accordance with Article 1(2), the Regulation does not apply to active principles of biological origin intended to produce active or passive immunity or diagnose the state of immunity used in immunological veterinary medicinal products. However, it should be noted that the Regulation does apply to pharmacologically active substances of non-biological origin, which are used in the manufacture of immunological veterinary medicinal products. Thus an application for the establishment of MRLs will be necessary in the case of pharmacologically active excipients or adjuvants used in veterinary sera or vaccines.

The CVMP has considered in detail the definition of pharmacologically active substances in the context of Directive 2001/82/EC, as amended, with a particular reference to excipients and manufacturing materials and has published a position paper on the matter (EMEA/CVMP/072/97-Revised). This position paper states, that for a particular veterinary medicinal product intended for administration to food-producing animals, any excipient, not having pharmacodynamic activity at the dose at which it is administered to the target animal by means of the veterinary medicinal product in which it is included does not need to have an MRL established as a prerequisite to the granting of a marketing authorisation for this product. However, the applicant must demonstrate the absence of such activity so that the inclusion of this excipient in Annex I, II or III of Regulation (EEC) No 2377/90 is not required. Such proof can be made at the time the application for a marketing authorisation is made and appropriate data shall be provided in the application submitted for the granting of a marketing authorisation for that veterinary medicinal product. Alternatively the applicant can request advice on the matter from the CVMP using the Scientific Advice procedure.

In case of doubt as to whether the establishment of MRLs will be required in respect of a particular substance or a specific use of that substance, the company responsible is advised to contact the EMEA as early as possible so that the advice of the CVMP can be obtained.

Where necessary, MRLs should be established for all the following food commodities from all species intended for human consumption including meat of mammals and poultry (muscle, fat, (fat and skin where appropriate) liver and kidney), meat of fin fish (muscle and skin in natural proportions), milk, eggs and honey.

However, it will not be necessary to establish MRLs in respect of substances, which are intended solely for use in non-food-producing animals, such as cats or dogs.

3. Types of MRL(s) and other outcomes of evaluation

It should be noted that Regulation (EEC) No 2377/90 envisages that at the end of an evaluation a pharmacologically-active substance may be inserted into one of four Annexes, three of which allow the use of the substance in food-producing animals.

Annex I of the Regulation contains the list of substances for which final MRLs have been established. This means that in the opinion of the CVMP complete and sufficient data are available for the safety evaluation of the substance concerned for the Commission to reach a final decision on MRLs.

Annex II contains the list of substances for which no MRLs are necessary because, at the time the evaluation is completed, residues of the substance concerned are not considered to present a public health risk from the levels used. A substance may only be proposed for insertion into Annex II after the evaluation of the safety of residues of the substance concerned. Thus a decision to insert a substance in Annex II has the same effect as the allocation of MRLs to a substance in Annex I. For this reason the expression "the establishment of MRLs" is used to cover the inclusion of a substance in Annex II. A recommendation to insert a substance in Annex II should not be interpreted as automatically implying that no withdrawal period is necessary. At the present time, decisions concerning withdrawal periods are taken on a case-by-case basis either by the Member States in the case of national or mutual recognition procedures, or by the Commission in relation to centrally approved marketing authorisations.

Provisional MRLs may be established for pharmacologically active substances, provided that there are no grounds for supposing that residues of the substance at the level proposed will present a hazard for the health of the consumer. Such provisional MRLs are to be inserted into Annex III of the Regulation for a defined period not exceeding five years.

Where it appears that an MRL cannot be established for a pharmacologically active substance used in veterinary medicinal products because residues of the substance concerned, at whatever concentration, in foodstuffs of animal origin constitute a hazard to the health of the consumer, that substance shall be included in the Annex IV. Veterinary medicinal products containing substances included in Annex IV are forbidden for treatment of food producing animals.

A further outcome of the evaluation may be the conclusion that insufficient data were present for evaluation to recommend inclusion in any of the four annexes. In effect, this also means that the substance may not be used for treatment of food producing animals. In short, the CVMP will in such a case conclude that the information was insufficient to determine safe residue limits.

II. Applications for the establishment of MRLs for pharmacologically active substances (Article 6 of Regulation (EEC) No 2377/90) as amended by Regulation (EC) No 1308/99)

1. Introduction

Point 1 of Article 6 of Directive 2001/82/EC, as amended, states[9]:

"*A veterinary medicinal product may not be the subject of a marketing authorisation for the purpose of administering it to one or more food-producing species unless the pharmacologically active substances which it contains appear in Annexes I, II, or III to Regulation (EEC) No 2377/90."*

In order to avoid potential delay which may arise from doubts about the safety of residues, applicants are strongly advised that it is in their own interest to submit an application for the establishment of MRLs to the EMEA as soon as the necessary documentation is complete, and before the submission of an application for marketing authorisation to the EMEA or (the individual) Member States. Article 12 of Directive 2001/82/EC, as amended, states:

"At least six months shall elapse between a valid application for the establishment of maximum residue limits and an application for a marketing authorisation."

2. Steps to be taken before the submission of an application

About 3-4 months before the anticipated date of submission of an application for the establishment of MRLs in respect of a particular substance, the applicant should contact the EMEA, indicating that the application is to be submitted in accordance with Council Regulation (EEC) No 2377/90, as amended, to:

EMEA
Unit for Veterinary Medicines and Inspections
Sector for Safety of Veterinary Medicines
7 Westferry Circus
Canary Wharf
London E14 4HB
United Kingdom

[9] OJ L136, 30.04.2004, p 58-84, coming into force by 30 October 2005.

The following information should be provided at this time:

- The name of the substance
- Chemical group to which it belongs
- Therapeutic category
- Proposed target species and indications
- Food commodities for which MRLs will be required
- Anticipated date of submission
- The name, address, fax and phone number of a contact point within the company which will be responsible for all correspondence between the company and the EMEA in respect of the application.

After the CVMP meeting at which the letter of intent is considered, the EMEA secretariat will notify the applicant of the procedural details (rapporteur, co-rapporteur (where appropriate), recommended submission dates etc.) in accordance with the Standard Operating Procedure (EMEA/CVMP/819/99-Rev.3 Submission and evaluation procedure for an application for the establishment of Maximum Residue Limits).

3. Preparation of the application

3.1 Full MRL Applications

3.1.1 Presentation of the dossier

The information required for the establishment of MRLs by the European Union is set out in Annex V of Regulation (EEC) No 2377/90, as amended by Commission Regulation (EEC) No 762/92. In order to facilitate the review of the dossier, it is proposed that this information is presented in two distinct parts of the dossier, a safety file and a residue file. A summary of the order of presentation required is set out in Part II, III.1 (General information). More detailed guidance on the preparation of the information required is provided in the "Guideline on the application of Annex V of Regulation (EEC) No 2377/90 with a view to the demonstration of the safety of a veterinary medicinal product." This guideline is reproduced in Part III of the present volume.

3.1.2 Expert Reports

The proposed structure for the dossier includes two separates expert reports; one covering the safety file and one covering the residue file.

The expert reports are of fundamental importance in facilitating the evaluation of the detailed documentation submitted in support of the application. Some guidance on the preparation of these expert reports is given in Part II, III.2 (Expert Reports) of the present volume.

Applications, which are not accompanied by expert reports, and applications with manifestly unsatisfactory expert reports will not be accepted.

3.1.3 Language

In principle, the application could be submitted in any of the official languages of the European Union. However, in view of the multi-lingual environment in which the Community operates, and considering the tight timelines, in which the CVMP has to evaluate the dossier, a submission in any other language than English would require translation by the applicant before it can be processed. It will greatly facilitate the evaluation of applications if the original data are provided in English. If data generated in another EU language or in a language from outside the EU are presented in the dossier, normally a translation of the study or a summary in English, as appropriate, will be requested in order to allow the data to be evaluated.

3.2 Extensions and modifications of existing MRLs

In the case of applications for the extension of existing MRLs to other animal species or specific food commodities, e.g. milk, eggs, usually a dossier consisting only of an application form and a residue file with regard to the relevant target species is required. The Expert Report should summarise the safety evaluation of the substance including reference to the existing ADI as well as to the MRLs, previously established.

In the case of applications for the modification of the ADI, the dossier should include an application form and the relevant safety data. The Expert Report should summarise the safety evaluation of the substance including reference to the existing ADI and review the new data supporting the modification of the ADI. Should the application include a request for modification of MRLs an Expert Report justifying the new MRL values proposed and any relevant residue data should be included.

4. Submission of the application

The application form set out on pages 36 to 37 must be completed and enclosed with each copy of the application.

Ideally, the application should be transmitted simultaneously directly to the EMEA, rapporteur and co-rapporteur. The application must be accompanied by the fee payable to the EMEA in accordance with Regulation (EC) No 275/97[10] as amended by Regulation (EC) No 494/2003[11]. Applicants are advised to use registered post with acknowledgement of receipt or a similar method of transmission. Applications are only considered as submitted to the EMEA when both the dossier and the fee have been received. The time period for validation will then start. The time limit for the evaluation only begins once the EMEA has validated the application and rapporteur and co-rapporteur have confirmed receipt of the application as validated. Following validation, applicants should also send the required information to the remaining CVMP members and alternates according to the requests specified in Annex II of the Standard Operating Procedure (EMEA/CVMP/819/99-Rev.3. Submission and evaluation procedure for an application for the establishment of Maximum Residue Limits). An up-to-date address list is provided by the EMEA prior to the submission.

5. Validation of the application

The validation will be undertaken by the EMEA, which has to proceed and complete the administrative validation, within 10 working days of receipt of the application. Applicants will be contacted by the EMEA, if it is considered that the application is not acceptable as such for evaluation. If the deficiencies can be resolved within a short period of time, the applicant will be advised of the steps, which must be taken to remedy the defects in the application. Otherwise the application will be considered invalid and rejected. In case where the application is considered invalid, an administrative charge of 1,500 Euro will be withheld by the EMEA.

Once the application has been validated, the EMEA will inform the applicant in writing.

6. Evaluation of the application

Regulation (EEC) No 2377/90 provides for a period of 120 days for the evaluation of the application, which is undertaken by the CVMP. In order to ensure optimal use of the 120 days period for the evaluation of the initial as well as any additional information, which may be requested after the initial assessment, the CVMP has endorsed the following time lines:

- Initial evaluation: within 90 days of receipt of a valid application
- Evaluation of additional information: within 30 days of receipt of the consolidated response

[10] OJ L 35, 15.2.1995, p. 1.
[11] O.J. L 73, 19.3.2003, p. 6.

After the initial evaluation and having regard to the recommendations of the CVMP, the EMEA Secretariat will transmit to the applicant either:

- A CVMP Opinion including an Assessment Report and Summary Report agreed in respect of the application, or
- A List of Questions included in a Status Report of the CVMP assessment to which the applicant is invited to reply.

If questions arise after the initial evaluation of the application, the 120-day time limit for completion of the evaluation laid down in the legislation is suspended until a reply is received from the applicant. The time frame given for the reply is normally 6 months. Upon a justified request from the applicant, this period may be extended.

When provisional MRLs are recommended following the completion of the evaluation the recommendation will include a list of questions to be addressed by the applicant in a timeframe that will be established on a case by case basis but will allow for a decision on the final MRLs to be taken well in advance of the expiry date of the provisional MRLs. Further to the submission of the response following the establishment of provisional MRLs a 90-day period for evaluation of the response is initiated

In each case a single consolidated response should be presented to all the questions. This response should follow the same structure as the initial application, and the same guidelines apply for its presentation and submission.

An updated expert report will be required if:

- Significant additional safety or residue information is submitted, or
- As a result of the questions and comments received, the applicant decides to amend the proposals for MRLs for the substance concerned.

As appropriate, the updated expert report may be presented as a supplement to the original report, or may be consolidated into the original report. However, in the latter case the changes made to the original report must be clearly identifiable, through underlining, sidelining etc.

The consolidated response must be submitted to rapporteur, co-rapporteur and EMEA. When an updated expert report accompanies the consolidated response (or an addendum to the expert report) it is sufficient to only submit the revision of or the addendum to the expert report(s) to the remaining CVMP members and alternates. In the absence of a revision or addendum to the export report(s), the complete consolidated response must be sent to all CVMP-members and alternates.

Applicants are strongly advised to co-ordinate the submission of the consolidated response with the EMEA secretariat. Furthermore, applicants are advised to submit the consolidated response to the List of Questions first to the rapporteur, co-rapporteur and the remaining CVMP members and alternates, allowing a period of at least 30 days before the consolidated response is submitted to the EMEA

secretariat. The procedure, i.e. the period of 30 days remaining for the evaluation of the additional information, will re-start on the first working day following the receipt of the response by the EMEA secretariat. The time between the submission of the response to the rapporteur and co-rapporteur and the submission to the EMEA will be used to evaluate the data. The 30 days remaining of the 120-day period are used for the necessary consultation of the CVMP members and for the Committee to reach its final opinion.

In principle, there are three possible conclusions of the evaluation:

- The CVMP recommends the establishment of MRLs (either final, or in exceptional cases provisional) or the inclusion in Annex II of Regulation No 2377/90;
- Because of the risks for public health presented by the substance the CVMP recommends that its use in food-producing animals be prohibited through inclusion in Annex IV of Regulation (EEC) No 2377/90;
- The CVMP, after evaluation of the additional information received as a consolidated response to a List of Questions issued further to the initial evaluation, or the recommendation of provisional MRLs, concludes that there is still insufficient information available for a recommendation for the inclusion of the substance in Annexes I, II or III of Regulation (EEC) No 2377/90, or into Annex IV, respectively.

A CVMP Opinion including an Assessment Report and Summary Report in such respect will be transmitted to the applicant following the CVMP consideration.

In all cases, in accordance with Article 7 of Regulation (EEC) No 2377/90, as amended, the applicant has the right to appeal against the Opinion.

Where no indication for an appeal is given to the EMEA within the 15 days after receipt of the Opinion, the Opinion becomes final and will be submitted together with the Summary Report and analytical method, where appropriate, to the European Commission within 30 days after adoption by the CVMP. The Commission will then prepare a draft Commission Regulation to amend Annex I, II, III or IV as appropriate and submit it to the Standing Committee on Veterinary Medicinal Products for adoption in accordance with the procedure laid down in Article 8 of Regulation (EEC) No 2377/90.

Where an appeal is received the final recommendation of the CVMP is only forwarded to the Commission after the consideration of the appeal.

7. Appeals

7.1 How to appeal against a CVMP Opinion

Where an applicant wishes to appeal against a CVMP opinion written notice of this intention must be provided to the EMEA Secretariat within 15 days of receipt of the Opinion. The day of the receipt is the day, when the Applicant receives the Opinion and Summary Report by fax.

Written detailed grounds for the appeal must be submitted within 60 days of receipt of the CVMP Opinion. Appeals and supporting grounds for appeals should contain argumentation and clarification of data previously submitted in the original application. It is not considered the purpose of an appeal to provide an opportunity for the submission of new data.

The CVMP will in such cases appoint a new rapporteur, (and where appropriate, a new co-rapporteur).

The detailed grounds for appeal shall be presented in one of the following ways:

- Attached to the written notice by the applicant to the EMEA secretariat of his intention to appeal against the CVMP Opinion (to be sent within 15 days after receipt of the CVMP Opinion); a copy should be sent to the rapporteur for the assessment of the appeal (and, where appropriate, to the co-rapporteur);
- Submitted separately to the EMEA Secretariat within 60 days of receipt of the CVMP Opinion and to rapporteur for the assessment of the appeal (and, where appropriate, to the co-rapporteur) (only if not more than approximately 20 pages);
- Submitted to the EMEA Secretariat and directly to all CVMP Members and alternates within 60 days of receipt of the CVMP Opinion (if more than approximately 20 pages).

Applicants are advised to contact the EMEA secretariat before the submission of the grounds for appeal to clarify the most suitable option. A copy of the grounds for appeal should be submitted to the rapporteur for the assessment of the appeal, (and, where appropriate, the co-rapporteur) at the same time as the submission to the EMEA is made. If in addition to the provision of the written detailed grounds for the appeal, an oral presentation of the case is requested, this should be indicated in writing to the EMEA.

7.2 Processing of the appeal by the EMEA

The CVMP will be informed by the Secretariat of receipt of the written notice of an intention to appeal at the next CVMP meeting following the receipt of the notice. The CVMP will appoint at this meeting the new rapporteur and, where appropriate, co-rapporteur for the assessment of the appeal. The CVMP will consider the appeal and agree on the final Opinion within 60 days (i.e. normally by the second CVMP meeting) following the receipt of the detailed grounds for the appeal.

The Committee shall invite the applicant to provide oral explanations to the Committee when the applicant requests these. The Committee may also invite on its own initiative the applicant to provide oral explanations. Nevertheless, such appearances before the Committee should be reserved to cases where the

Committee considers that these will contribute to the resolution of the objections raised by the applicant. In particular, the written detailed grounds for the appeal and reason for the request of an oral explanation must always be submitted first.

In the case of a hearing, copies of the presentation and short CVs of the applicant's representatives should be submitted to the EMEA prior to the meeting.

III. General information

1. Information to be provided in an application for the establishment of MRLs for a pharmacologically active substance to be used in veterinary medicinal products

An application for the establishment of MRLs should be prepared in accordance with the order of presentation given below (equivalent to Annex V of Regulation (EEC) No 2377/90, as amended).

All volumes should be clearly numbered and paginated. Continuous pagination of the complete dossier is the best option. Particular care should be taken to ensure that there is adequate cross-referencing between volumes and between the expert report and the original data.

Where reference is made to publish information, complete copies of the relevant articles should be inserted at the relevant point of the documentation.

The dossier shall comprise:

- An application form (bearing the original signature of the applicant): (see page 36 to 37 of this volume);
- A Safety and a Residue File including expert reports (bearing the original signature of the expert(s)).
- A copy of the completed application form should also be inserted at the beginning of the Safety File and the Residue File, as often-different experts will evaluate the two parts of the dossier.

Where the extension of existing MRLs to other animal species or specific food commodities, e.g. milk, eggs, is requested, normally only a dossier consisting of an application form and a residue file shall be submitted. In the Expert Report reference should be made to the existing ADI and previously established MRLs.

Contents of the dossier

A. Safety file

A.0. Expert Report
Presented in accordance with the guidance given in section 2 of this chapter

A.1. Precise identification of the substance concerned by the application

1.1 International non-proprietary name (INN)

1.2 International Union of Pure and Applied Chemistry (IUPAC) name

1.3 Chemical Abstract Service name

1.4 Classification

- Therapeutic
- Pharmacological

1.5 Synonyms and abbreviations

1.6 Structural formula

1.7 Molecular formula

1.8 Molecular weight

1.9 Degree of impurity

1.10 Qualitative and quantitative composition of impurities

1.11 Description of physical properties

- Melting point
- Boiling point
- Vapour pressure
- Solubility in water and organic solvents expressed in g/l, with indication of temperature
- Density
- Refractive index, rotation etc.

A.2. Pharmacology

A summary of the results of the various pharmacological studies, with particular emphasis on results which may be relevant to the evaluation of the safety of residues of the substance.

A.2.1 Pharmacodynamics

A.2.2 Pharmacokinetics

A.3. Toxicological studies

3.1 Single dose toxicity

3.2 Repeated dose toxicity

3.3 Tolerance in the target species of animal

3.4 Reproductive toxicity, including teratogenicity

3.4.1 Study of the effects on reproduction

3.4.2 Embryotoxicity/foetotoxicity, including teratogenicity

3.5 Mutagenicity

3.6 Carcinogenicity

A.4. Studies of other effects

4.1 Immunotoxicity

4.2 Neurotoxicity

4.3 Microbiological properties of residues

4.3.1 Potential effects on the human gut flora

4.3.2 Potential effects on the micro-organisms used for industrial food processing

4.4 Observations in humans

A5 Safety evaluation of residues

5.1 Proposal for an acceptable daily intake (ADI)

5.2 Alternative limits

5.3 When no limit can be set

B. Residue File

B.0. Expert report

Presented in accordance with the guidance given in section 2.

B.1. Precise identification of the substance concerned by the application

The substance concerned should be identified in accordance with point A. 1. However, where the application relates to one or more veterinary medicinal products, the product itself should be identified in detail, including:

- Qualitative and quantitative composition;
- Purity;
- Identification of the manufacturer's batch used in the studies; relationship to the final product;
- Specific activity and radio-purity of labelled substances;
- Position of labelled atoms on the molecule.

B.2. Residue studies

2.1 Pharmacokinetics (absorption, distribution, metabolism, excretion)

2.2 Depletion of residues

2.3 Elaboration of MRLs

B.3. Analytical method for the detection of residues

3.1 Description of the method

3.2 Validation of the method

- Specificity
- Accuracy
- Precision
- Limit of detection
- Limit of quantification
- Practicability and applicability under normal laboratory conditions
- Susceptibility to interference
- Stability

2. Expert Reports

2.1 General Principles

In accordance with Annex V of Regulation (EEC) No 2377/90 as amended the information and particulars submitted in support of an application for the establishment of MRLs should include Expert Reports. Applications submitted without Expert Reports or with manifestly inadequate Expert Reports will be considered invalid.

It is important to emphasise that well-prepared Expert Reports facilitate the process of evaluation of applications and particular care should be taken in their preparation.

An Expert Report should consist of a critical discussion of the properties of the substance under review. The expert is expected to take and defend a clear position on the adequacy of the safety and/or residue evaluation of the substance concerned, which has been undertaken by the applicant, in the light of current scientific knowledge. A simple summary of the documentation is not adequate.

Since the purpose of preparing an Expert Report is to facilitate the task of the rapporteur and co-rapporteur in the evaluation of the application, suitably qualified and experienced persons must be used. Authors of reports should be chosen only on the basis of their qualifications and experience. If the individual preparing the Expert Report is an employee of the applicant, it is essential that they be given sufficient authority to undertake the task, including a critical discussion of various investigations carried out. The expert does not necessarily have to have been personally involved in the performance of the tests.

The applicant delegates to the expert the task of preparing a critical view of the relevant part of the application on its behalf. However, the applicant remains primarily responsible for the whole application, including the Expert Reports.

Before preparing an Expert Report, the expert should consult the requirements of Directive 2001/82/EC, as amended, on the Community code related to veterinary medicinal products and the requirements of Regulation (EEC) No 2377/90. In addition the expert should consider the guidance given below.

The expert must be given full access to all the data collected by the company concerning the substance under review.

All-important data should be summarised in an annex to the Expert Report and, whenever possible, should be presented in tabular or graphic form. (See Volume 6B pages 75-115 for models of tabular study reports). Where the expert does not prepare the summary of important data himself, he must undertake a full review of the original data and endorse the accuracy of the summary.

In order to facilitate the evaluation of the application, two separate Expert Reports are to be submitted, one for the safety file and one for the residue file. Each report will normally be less than 25 pages, followed by the summary tables and bibliographical references.

An Expert Report should bear the original signature of the expert(s) and the place and date of its issue. Attached to the report should be brief information on the expert(s), their name(s), educational background, training and occupation. The professional relationship of the expert to the applicant should be clearly stated.

2.2 Safety File

The Expert Report on the safety file should comprise a critical evaluation of the studies undertaken to investigate the pharmacological, toxicological and other properties of the substance, and should conclude with a discussion of all the results observed and a proposal for an ADI. This Expert Report should be prepared in accordance with the guidance given in point 2.2.1 below.

In addition, as mentioned above, a series of annexes to the Expert Report should provide bibliographical references, tabulated summaries of data and brief biographical information about the expert. Guidance on the preparation of the Annexes is given in point 2.2.2 below.

2.2.1. Expert Report on the Safety File

The introduction should describe the actual or proposed pattern of use of the substance under review in veterinary medicine, and summarise any other experience in its use.

The expert should also consider the extent to which the substance concerned has analogies with other known substances, which may be relevant for the purpose of evaluation.

The expert should comment on the Good Laboratory Practice (GLP) status of the studies submitted. Attention should be drawn to possible deficiencies in the design and conduct of the studies and their documentation.

The expert should present a critical evaluation of the experimental studies and an interpretation of the results. Relevant scientific literature should be taken into account for the evaluation. If detailed references to published scientific literature are to be used, all the requirements set out below for study report(s) should be met, as far as possible.

Information on the quality of batches of test substances used in the safety studies must be provided. Any association between findings and the quality of the test substances and/or the medicinal products should be indicated. The expert should, when necessary, present a critical evaluation of the impurities present in the active ingredient and give information on their potential biological effects. The implications of any differences of the chirality, chemical form and impurity profile between the substance used in the safety studies and for the form to be marketed should be discussed.

In particular, in each case the expert should refer to the following:

- The effects of an active ingredient observed in the safety studies in relation to those expected or observed in human beings (as potential consumers of residues in food of animal origin), in particular;
- Potential effects during pregnancy and lactation;
- Mutagenic effects;
- The carcinogenic risk. If relevant epidemiological data are available they should be taken into account;
- Possible (other) irreversible toxic effects.

Justification for the omission of particular studies (e.g. carcinogenicity studies) should be given. Requirements for additional studies should be discussed.

The Expert Report must contain page references for each relevant tabulated study report and/or the written summaries annexed to the Expert Report. The tabulated study reports and/or the written summaries in turn should indicate the page references to the basic documentation.

2.2.1.1. Pharmacology

Pharmacodynamics

Studies conducted to establish the pharmacodynamic effects (including both desired therapeutic effects and secondary pharmacological effects) and the mode of action should be evaluated here, if they are relevant for the safety evaluation of residues in food.

For some substances the NOEL/LOEL, used as the basis for estimation of the overall ADI, could be based upon a pharmacodynamic effect if this occurred at doses lower than those required to elicit toxicity or adverse antimicrobial effects on the human gut flora.

Pharmacokinetics

The data on absorption, distribution, biotransformation, excretion, and the occurrence of metabolites in laboratory animals, target animals (where relevant), and in humans (where available) should be assessed in view of the necessary extrapolations from animals to the human consumer of residues. The relevance of the following should be considered:

- The methods used (including sensitivity and validation of assays);
- The pharmacokinetic models;
- The pharmacokinetic parameters.

2.2.1.2. Toxicology

The onset and duration of the toxic effects, the dose dependency and the reversibility or irreversibility, and all species-related or sex-related differences should be reviewed and discussed, in particular:

- Toxic signs;
- Causes of death;
- Clinical-chemical, haematological, pathological, and all other relevant findings.

If the dose-response relationship changes, e.g. with increasing doses or upon repeated/long-term dosing, an explanation should be proposed.

Extrapolation of the data from animal species to humans should be discussed considering the:

- Animal species used;
- Number(s) of animals used;
- Route(s) of administration employed;
- Dosage(s) used;
- Duration of treatment and/or of the entire study**;**
- The dose-response relationship;
- The nature of the adverse effects.

If alternatives to whole-animal experiments are employed, their validity should be proved.

Single dose toxicity

If single dose toxicity data are available, the toxic phenomena (both functional and morphological) and their occurrence related to time, dose level, and route of administration should be reviewed.

Repeated dose toxicity

The toxic phenomena (both functional and morphological) and their occurrence related to time, dose level, and route of administration resulting from the repeated administration of the test substance (active ingredient or, where necessary a metabolite thereof) should be reviewed.

The length of the period of exposure shall be critically reviewed considering possible exposure to residues of human consumers. A justification should be given for the (NOEL/LOELs proposed for each study.

Tolerance in the target species of animal

The results of tolerance trials should be discussed here if they provide information relevant to the safety evaluation of residues.

Reproductive toxicity including developmental toxicity

The potential to adversely influence reproductive performance of exposed adults as well as the normal development of their progeny should be reviewed.

If embryotoxic, fetotoxic or teratogenic effects were observed, an interpretation of their significance in view of the safety of the human consumer is necessary. An NOEL/LOEL should be proposed for each study and the reasoning behind the choice of each should be explained**.**

Mutagenicity

The potential of the active ingredient and/or its relevant metabolites to cause changes in the genetic material should be assessed on the basis of the documentation and in the light of known structure-activity relationships. The expert should also express his views on the adequate selection of the test batteries with respect to their predictive value and the spectrum of potential mutagenic events covered**.** The relevance of the results of the mutagenicity tests to potential carcinogenicity of the substance should be discussed.

Carcinogenicity

The expert should evaluate the potential carcinogenicity of the active ingredient and/or its metabolites based on the documentation. The expert should particularly consider the structure of the substance(s) and its (their) relationship to the structure of known carcinogens, data from short-term genetic toxicity testing, results from both short-term and long-term feeding studies, and any other available information (e.g., covalent binding to cellular macromolecules).

The expert should draw specific attention to observations such as an increase in the incidence of tumours as compared with the untreated control animals, the development of tumours earlier than in the control animals, the occurrence of types of tumours usually not seen in untreated control animals, the malignancy of tumours, and the appearance of pre-neoplastic lesions.

Whenever possible, the (suspected) mechanism of carcinogenicity should be discussed together with the possibility of determining whether the mechanism is likely to be a threshold-limited process.

2.2.1.3. Other Requirements

These tests are required to address safety concerns such as those based on compound structure, class and mode of action. Some examples of these studies are:

Immunotoxicity

The expert should critically examine whether toxicological manifestations in experimental animals during toxicity testing indicated effects on the immune system and whether such effects have been addressed.

Neurotoxicity

The neurotoxic effects of substances with potential to have adverse effects on the nervous system should be discussed. Such substances include, for instance, avermectins, pyrethroids, organophosphates and carbamates. For organophosphates and carbamates neurotoxicity should be addressed with particular reference to effects on cholinesterase activity. Delayed neurotoxicity and effects on neuropathy target esterase (NTE) should also be addressed for organophosphates.

Microbiological properties of residues

The expert should consider both the potential effects of the substance on the human gut flora of the consumer and any potential effects on the micro - organisms used in the industrial processing of foodstuffs.

Potential effects on the human gut flora

The expert should evaluate the results of studies conducted in accordance with the VICH guideline 36 (CVMP/VICH/467/03) that is implemented in the European Union since May 2005. Where effects of residues of the substance on the human gut flora are demonstrated, a microbiological ADI may be established.

Potential effects on the micro-organisms used in the industrial processing of foodstuffs

The expert should evaluate the documentation on the effects of low concentrations of microbiologically active residues, particularly in milk, on the preparation of yoghurt and cheese and other microbiologically based food-technology processes. An NOEL should be proposed. This NOEL should be taken into account when milk MRLs are proposed.

Observations in humans

The relevance to the safety evaluation of the active ingredient of any documented epidemiological, pharmacological, toxicological and/or clinical human data should be discussed.

2.2.1.4. Conclusions

The expert should summarise the documentation, which is considered relevant for the assessment of consumer safety. The results of the safety studies should then be extrapolated to humans and an acceptable daily intake (ADI) or alternative limit should be derived.

The expert should comprehensively discuss the proposals made.

If applicable, the expert should also identify a concentration without effect on the industrial processing of foodstuffs obtained from treated animals.

2.2.2. Appendices to the Expert Report on the safety file

2.2.2.1. List of references

A list of references used, should be given and stated in accordance with internationally accepted standards.

2.2.2.2. Tabulated study reports

A complete set of study reports is included in the dossier. In order to facilitate assessment, applicants should append tabular representations of study reports to the Expert Report.

The results of the following studies should be presented in tabular form:

- Pharmacodynamics
- Pharmacokinetics
- Biotransformation
- Single dose toxicity
- Repeated dose toxicity
- Chronic toxicity
- Developmental toxicity (embryotoxicity/fetotoxicity/teratogenicity)
- Reproduction toxicity (multigeneration studies)
- Mutagenicity

- Carcinogenicity
- Special studies (e.g. microbiology, neurotoxicity).

2.2.2.3. Information on the expert

The qualifications and experience of the safety expert should be briefly summarised. The professional relationship of the expert to the applicant should be stated.

2.3 Residue File

The Expert Report on the residue file should comprise a critical evaluation of the studies undertaken to investigate presence and persistence of residues of the substance under investigation and should conclude with a discussion of all the results observed, and proposals for MRLs for the substance concerned in all relevant food commodities. This Expert Report should be prepared in accordance with the guidance given in point 2.3.1 below.

In addition, a series of Annexes to the Expert Report should provide bibliographical references, tabulated summaries of data and brief biographical information about the expert. Guidance on the preparation of the Annexes is given in point 2.3.2 below.

2.3.1. Expert Report on the Residue File

The introduction should describe the proposed pattern of use of the substance under review in veterinary medicine, and summarise any other experience in its use.

The expert should comment on the GLP status of the studies submitted. Attention should be drawn to possible deficiencies in the design and conduct of the studies and their documentation.

The expert should present a critical evaluation of the experimental studies and an interpretation of the results. Relevant scientific literature should be taken into account for the evaluation. If detailed references to published scientific literature are to be used, all the requirements set out below for study report(s) have to be met.

In respect of each study, the expert should specifically refer to the following:

- Animals used in pharmacokinetic and residue depletion studies (species, strain, sex, age, weight, etc.)
- The test substances used (number of the batch, quality etc.); information on the quality of batches used in analytical and residue studies must be provided. Any association between findings and the quality of the test substances and/or the medicinal products should be indicated. The expert should, when necessary, present a critical evaluation of the impurities present in the active ingredient and give information on their potential influence on pharmacokinetics, metabolism, residue kinetics and

analytical methods for the determination of residues. The implications of any differences in the chirality, chemical form and impurity profile between the substance used in the residue studies and for the form to be marketed should be discussed;

- Test conditions (husbandry, diet, etc.);
- Milk- and egg-production (if applicable);
- Sampling (sample size; collection and storage, etc.);
- Analytical methods used.

Justification for the omission of particular studies should be given. Requirements for additional studies should be discussed.

The Expert Report must contain page references for each relevant tabulated study report and/or the written summaries annexed to the Expert Report. The tabulated study reports and/or the written summaries in turn should indicate the page references to the basic documentation.

2.3.1.1. Metabolism and residue kinetics

Absorption, distribution, metabolism, excretion

The data on absorption, distribution, biotransformation, excretion, and the occurrence of metabolites in food-producing animals should be summarised and assessed in view of the tissue residue characteristics of the substance concerned. The chemical nature and concentrations of the residues in edible tissues (muscle or muscle plus skin in natural proportion, fat or fat plus skin, liver, kidney, milk, eggs, honey) should be summarised. Marker residue(s) for each edible tissue and product and MRL values should be proposed. Target tissue(s) should be defined as indicated under point B.I.3.1. In the event that chemically bound residues are formed, the expert should discuss all available information on mechanisms and reversibility of their formation and, if relevant for the final assessment, their bioavailability following oral ingestion. The validity of the methods used in the context of the above studies should be reviewed.

Depletion of the residues of concern

The expert should summarise the time-course (including kinetic parameters) of the depletion of the relevant residues (e.g. total residue and/or marker residue) in all standard edible tissues as defined on page 61 of this document. The suitability of these studies to serve as a basis for the calculation of withdrawal times should be commented upon.

2.3.1.2. Maximum Residue Limits

The expert should propose MRLs for all relevant pairs of marker residue and edible tissue taking into account the safety data and the proposed ADI. The proposed MRLs must meet the requirements laid down in Regulation (EEC) No 2377/90 as amended. The expert should refer to the CVMP guidelines and position papers in relation to the setting of MRLs for minor animal species, fish and milk (EMEA/CVMP/153a/97 – Note for Guidance on the Establishment of Maximum Residue Limits for Minor Animal Species, EMEA/CVMP/153b/97 – Note for Guidance on the Establishment of Maximum Residue Limits for *Salmonidae* and other Fin Fish, EMEA/CVMP/391/02 – Position Paper on the establishment of MRLs for Milk considering the daily intake by children).

The expert should estimate the proportion of the ADI resulting from consumption of food basket amounts of the relevant tissues/products containing residues at the proposed MRL values. In particular, when substances are also used in plant protection products (i.e. pesticides) this should be taken into account (see point B.I.1.).

Where the Joint FAO/WHO Expert Committee for Food Additives (JECFA) has already undertaken an evaluation of the substance and recommended MRLs to the Codex Alimentarius Committee for Residues of Veterinary Drugs in Foods (CCRVDF), the JECFA proposal or the Codex MRL should be summarised; and in case of proposing to deviate from it, this deviation should be explained.

2.3.1.3. Withdrawal Periods

Where relevant for the proposals for MRLs the expert should present and discuss a summary table of approximate withdrawal periods for each species of food-producing animal as well as their edible products, such as milk , eggs and honey, which could be realistically observed under conditions of good practice in the use of veterinary medicinal products. The expert should refer to the relevant CVMP guidelines and software in relation to the establishment of withdrawal periods in presenting these data (EMEA/CVMP/036/95 – Note for Guidance: Approach towards Harmonisation of Withdrawal Periods for meat, EMEA/CVMP/563/02 – Updated Application Software relating to Note for Guidance on Approach towards Harmonisation of Withdrawal Periods for Meat, EMEA/CVMP/473/98 – Note for Guidance for the Determination of Withdrawal Periods for Milk, EMEA/CVMP/231/00 *Rev. 1* – Updated Application Software relating to Note for Guidance for the Determination of Withdrawal Periods for Milk).

2.3.1.4. Analytical method for the determination of residues

The expert should ensure that validated analytical method(s) are available for the enforcement of the proposed MRLs when monitoring residues. In particular, relevant performance characteristics should be considered, such as specificity, accuracy, precision, limit of detection and limit of quantification.

2.3.1.5. Conclusions

The expert should clearly indicate in the conclusions that the proposed MRLs have been correctly derived and will not result in exceedance of the ADI that has been established under foreseeable conditions of use. The analytical method should be appropriate and fully validated, or, any deficiencies should be fully justified.

2.3.2. Appendices to the Expert Report

2.3.2.1. List of references

A list of references used should be given and stated in accordance with internationally accepted standards.

2.3.2.2. Tabulated study reports

A complete set of study reports is included in the dossier. In order to facilitate assessment applicants should append tabular representations of study reports to the Expert Report.

2.3.2.3. Information on the expert

The qualifications and experience of the safety expert should be briefly summarised. The professional relationship of the expert to the applicant should be stated.

APPLICATION FORM

APPLICATION FOR THE ESTABLISHMENT OF MRL(s) FOR AN ACTIVE SUBSTANCE TO BE USED IN VETERINARY MEDICINAL PRODUCTS IN ACCORDANCE WITH COUNCIL REGULATION (EEC) No. 2377/90 AS AMENDED

PART I: Administrative Data

Rapporteur:
Co-rapporteur:
Name of Substance for review, using INN (where attributed):
Name and address of applicant:
Please summarise the anticipated pattern of veterinary use: Target Species Major indications Dose regimen
Is the substance used in veterinary medicinal products as - active ingredient - excipient, preservative, etc?
Name, address, telephone number and fax number of company contact point for all correspondence arising in connection with the application:

PART II: SUMMARY OF THE EVALUATION PROPOSED BY THE APPLICANT

Name of substance for review:
Is this application for inclusion in: - Annex I (MRL values) - Annex II (no MRLs necessary)
Indicate the most relevant NOEL for the evaluation of the safety of residues (mg/kg bw/day):
Reference to relevant study (including location in the dossier):
Uncertainty factor proposed:
ADI proposed (mg/kg bw):
ADI x 60 = (acceptable daily intake per adult; mg)
MRLs proposed (µg/kg) MRL Food Commodity Marker Residue
Method of analysis proposed for residue monitoring Method: Limit of quantification: Reference (including location in the dossier):

I hereby certify that all information relating to the establishment of MRLs for the above-mentioned substance, whether favourable or unfavourable, has been submitted with this application.

Date Signature

PART III - Guideline on the application of Annex V of Regulation (EEC) No 2377/90 with a view to the demonstration of the safety of a veterinary medicinal product

Introduction

In accordance with Point 1 of Article 6 of Directive 2001/82/EC, as amended, a " veterinary medicinal product may not be the subject of a marketing authorisation for the purpose of administering it to one or more food-producing species unless the pharmacologically active substances which it contains appear in Annexes I, II, or III to Regulation (EEC) No 2377/90".

The purpose of this guideline is to provide the veterinary pharmaceutical industry with specific guidance on the design and conduct of the various types of tests and trials necessary to demonstrate the safety of residues of a veterinary medicinal product and to communicate the scientific approach for the establishment of MRLs applied by the CVMP to the applicants and the assessors.

The data requirements and content of a dossier in support of an application for the establishment of MRL in accordance with Regulation (EEC) No 2377/90, as amended, are laid down in Annex V of the aforementioned Regulation and described in Part II, section III above. The dossier comprises two main parts, a safety and a residue file.

The safety file contains the results of the pharmacological and toxicological studies conducted on the veterinary medicinal product.

The purpose of pharmacological studies is two-fold:

- To demonstrate the response of living organisms to the actions of the substance or its active ingredient(s) relative to its proposed use (pharmacodynamics);
- To provide a description of changes in concentration of the substance, or metabolites within the body (pharmacokinetics).

The pharmacological documentation to be provided in the safety file should be restricted to that which is relevant for the safety evaluation of the substance. More complete pharmacological documentation will be required in the residue file of the application.

The main purpose of the toxicological documentation is to demonstrate that under the proposed conditions of use, the veterinary medicinal product does not present any unacceptable risk to the consumer of foodstuffs obtained from treated animals. In addition, documentation may be required to show that no drug-related residues are found in products from treated animals which might cause difficulties during the subsequent processing of the product or lower directly the quality of the edible product.

The residue file contains the additional data necessary to determine MRLs based on the results contained in the safety file. These data include detailed investigations of the elimination of residues from edible tissues and other food products of animal origin, and proposals for methods for the analysis of residues.

A. Safety File

I. General considerations

1. Safety of the consumer

Testing of a specific substance contained in a veterinary medicinal product intended for the administration to food-animals should be designed taking into account:

- The proposed use of the substance in animal husbandry;
- The pharmacological activity of the substance, including pharmacodynamics and pharmacokinetics;
- The likelihood of the formation of relevant residues of the product (parent substance plus active metabolites);
- The probable exposure of the consumers to the residues remaining in foods derived from treated animals;
- The possible biological effects of the residues:
    - As observed in suitable biological *in vivo* systems,
    - As observed in suitable *in vitro* systems,
    - As deduced from structure-activity relationships.

Testing is normally required for the parent substance. However, separate testing of a metabolite may be required when necessary to define adequately the biological effects of the residue left in food intended for human consumption.

The following toxicological studies are required for each new substance:

- Repeated dose 90-day oral studies both in a rodent species (usually the rat) and in a non-rodent mammalian species (usually the dog);
- Repeated dose (chronic) toxicity studies, unless demonstrated to be not necessary, in at least one species, determined to be the most appropriate on all the available scientific data. The default species is the rat;
- A two-generation reproduction study in a rodent species, preferably the rat.

- Developmental toxicity testing should be conducted following a tiered approach. If a negative or equivocal result for teratogenicity is observed in the rat, a test in a second species, preferably the rabbit, is required. If the substance is teratogenic in the rat, a study in a second species is only necessary if it is evident from all the available data that teratogenicity will determine the ADI;
- A battery of mutagenicity studies.

Additional studies may be required as follows:

- Carcinogenicity studies;
- Other special tests (e.g. immunotoxicity, neurotoxicity**,** microbiological tests on the flora of the human gut).

From the results presented in the Safety File an acceptable daily intake (ADI) based on the most appropriate no observed effect level (NOEL) or no observed adverse effect level (NOAEL) , or in some cases from the lowest observed effect level (LOEL) should be derived. For substances with antimicrobial activity, the ADI would be set on the basis of microbiological data if these indicate a lower ADI than would be set on the basis of toxicological and pharmacological data.

2. Effects on the industrial processing of foodstuffs

In certain cases it may be necessary to assess whether the residues of the substance cause a variation in the quality of the food commodities concerned. In particular in the case of antimicrobial substances intended for administration to milk-producing animals, it may be necessary to carry out tests to determine whether residues may affect technological processes used in food processing.

3. Performance of tests

Tests shall be planned in such a way that the necessary information is acquired using the least possible number of test animals considering Council Directive 86/609/EEC, as amended, on the approximation of laws, regulations and administrative provisions of the Member State regarding the protection of animals used for experimental and other scientific purposes[12].

All safety studies shall be conducted in conformity with the principles of Good Laboratory Practice (GLP) recognised by Community legislation in Directives 87/18/EEC[13] and 88/320/EEC[14] as amended.

[12] OJ L 358, 18.12.1986, p. 1.
[13] OJ L 15, 17.1.1987, p. 29.
[14] OJ 145, 11.6.1988, p. 35.

As far as possible tests shall be conducted in accordance with internationally recognised and regularly updated test protocols, e.g. those recommended by the OECD, as written down in the Commission Directives 84/449/EEC[15] or 87/302/EEC[16] as amended, and/or fully described.

NOEL/LOELs employed, as the basis for ADIs should be based on the results of studies using oral dosing and conducted in accordance with current CVMP/VICH guidelines. Only in the exceptional case where the oral route is not appropriate, may other routes of administration be used.

4. Reporting of results

Documentation presented should name the laboratory where the work was performed and should be signed and dated**.** Summaries not accompanied by the individual data will not be accepted as valid documentation. Design, methods and conduct of the studies, name and qualifications of investigator, place and period of time the study was undertaken should be obvious from the test reports. The experimental techniques shall be described in such detail as to allow them to be reproduced, and the investigator shall establish their validity. All abbreviations and codes irrespective of whether they are internationally accepted or not should be accompanied by a key.

Test reports should include the following information (where applicable):

- Chemical identification of the test substance**,** including the isomer ratio and the enantiomers, if appropriate***;***
- Purity of the test substance;
- Stability, including stability in vehicle and feed when administered;
- For administration of the test substance other than in the diet or drinking water: the characteristics of the vehicle**,** including toxicological characteristics;
- Species, strain and source of test animals used, use of specific pathogen free animals, sex of the dosed animals, age of the animals at the beginning of the dosing;
- Dose levels and route and frequency of administration (with dosage in mg/kg bodyweight/day), test period, parameters followed, frequency of observation;
- Diet and environmental conditions;
- Description of toxic signs with the inclusion of time of onset, degree and duration;
- Results of the clinical observations, gross necropsy, and histopathology and of all other parameters investigated;

[15] OJ 251, 19.9.1984, p. 1.
[16] OJ L 133, 30.5.1988, p.1.

- Summaries of data in tabular form, showing for each test group and sex the number of animals at the start of the test, the number of animals showing drug related changes, the types of changes and the percentage of animals displaying each type of change;
- If possible, an estimate of a NOEL or LOEL.

All observed results should be evaluated by an appropriate (statistical) method and discussed in conjunction with other studies. A final judgement shall be given taking into account data from literature.

5. Further guidance

The CVMP has developed a number of further guidance documents in the form of guidelines, notes for guidance or position papers where specific problems need to be addressed. Also, in the process of International cooperation on harmonisation of technical requirements for registration of veterinary medicinal products between Japan, United States of America and Europe (VICH), relevant guidelines have been developed replacing where appropriate the concerned CVMP Guidelines. VICH Guidelines are available on VICH web site (http://vich.eudra.org/).

These documents outline how specific problems (data requirements for minor species, etc.), should be addressed and what else needs to be taken into consideration when compiling a dossier in support of an application for establishment of MRLs. The current versions of such guidance documents are listed at the end of this volume and are available on the EMEA web-site (http://www.emea.eu.int).

II. Specific requirements

1. Precise identification of the substance or product concerned covered by the application

The substance subject of the application should be clearly and specifically identified in accordance with the requirements laid down in Regulation (EEC) No 2377/90, as amended and/or Directive 2001/82/EC, as amended.

Adequate specifications should exist for the substance (batch) being tested, including purity (concentrations of impurities), isomer ratios and enantiomers**,** solubility and any other factor, which may influence its activity. Each batch used in the tests should be identified. Whenever possible, the test substances should have the same pattern of component chemicals and impurities as the substance to be marketed. Should the final dosage form have significantly different impurities, further investigation is required.

2. Pharmacology

Pharmacological studies can sometimes help in the understanding of toxicological phenomena. Pharmacodynamic studies may aid the interpretation of adverse effects arising from an exaggerated pharmacological response whilst knowledge of absorption, distribution, biotransformation and excretion may aid the assessment of routine toxicological studies.

For some substances the NOEL/LOEL, used as the basis for estimation of the overall ADI, could be based upon a pharmacodynamic effect if this occurred at doses lower than those required to elicit toxicity or adverse antimicrobial effects on the human gut flora.

2.1 Pharmacodynamics

The pharmacodynamic investigations can provide useful information on the mode of action and effects on organs and tissues. Studies should be provided that clearly identify both the primary (intended) and secondary (side effects) pharmacodynamic effects of the test substance. Such studies should clarify the dose-response relationship and identify a NOEL, where possible. For some substances (e.g. those with a history of use in human medicine) there may be human data available. These are usually the most useful data for use in identifying a pharmacological NOEL for the purpose of proposals for an ADI. In the absence of human data, laboratory studies should be performed using an appropriate animal model.

2.2 Pharmacokinetics (Absorption, Distribution, Metabolism and Excretion)

Pharmacokinetic investigations provide information on the absorption of a substance, its distribution and persistence in the tissues, its metabolism and excretion. In the Safety File, pharmacokinetic data (obtained mainly from studies in laboratory animals) model the fate of the substance when ingested by humans. The oral route should be the main route of administration in the pharmacokinetic studies. These studies can also help to explain unusual results obtained in toxicity studies, such as an apparent lack of dose-response when the drug is not well absorbed.

Pharmacokinetic data are required as part of the Residues File as well as in the Safety File. In the Residues File, pharmacokinetic data generated in the target species play an important role in identifying the metabolites that will occur as residues in food derived from the treated animals. A comparison of the metabolic profiles in the laboratory animal species used and the target animal species, and if available the metabolism in humans, is important to determine the relevance of the toxicological effects and NOELs observed in the experimental safety studies.

3. Toxicology

A full set of toxicological data will usually be required for substances, which have not previously been used in veterinary medicine. On the other hand, only a limited investigation would frequently be necessary, for example, for a new salt or ester of a toxicologically well characterised substance with a known safety profile. The material to be tested will usually be the substance included in the veterinary medicinal product, but when residues in foods derived from treated animals include significant amounts of a metabolite of specific toxicological concern it may be necessary to assess the toxicity of the metabolite, unless pharmacokinetic data indicates comparable exposure to the metabolite in the experimental animal species and target animal species.

Animal studies should be performed in established strains of laboratory animals for which historical data are available. Ideally, each substance should be tested in the strain and species of animals that is the best model for its effects in humans. However, as human data are not always available for comparison, it may not be possible to identify such animals. Then the most sensitive strain/species should be used for the determination of the ADI.

The CVMP has given advice in its position paper on the definition of substances capable of pharmacological action (document EMEA/CVMP/072/97-Revised, available on the EMEA web-site), with particular reference to excipients and manufacturing materials. Substances should be considered as pharmacologically active, if they exert pharmacological effects at the dose at which they are administered to target animals of the veterinary medicinal product(s) in which they are contained. Substances used in the manufacturing process of the active ingredients, which are not intended to be present in the final product, but of which traces only might be present, are considered as not falling within the scope of Council Regulation (EEC) No 2377/90.

Additional information outlining the safety testing of residues of veterinary drugs in food is given in CVMP-VICH Guideline 33: Safety Studies for Veterinary Drug Residues in Human Food: General Approach to Testing.

3.1 Single dose toxicity (acute toxicity)

Single dose studies to assess acute toxicity are not necessary in the identification of ADIs for veterinary medicinal substances and are not included in the current VICH guidelines. Usually acute toxicity studies will have been performed to obtain information on other aspects of safety (e.g. operator safety), and any reports of such studies should be submitted as part of the Safety File.

3.2 Repeated dose oral toxicity

Repeated dose oral toxicity testing means a qualitative and quantitative study of the toxic phenomena that may result from the administration of the test substance(s) and their occurrence related to time.

The aim of studies of repeated dose toxicity is the evaluation of functional and morphological changes due to repeated administration of the test substance(s) and to determine how these changes are related to dosage. In specific cases it may be of interest to demonstrate whether the effects are reversible or not.

3.2.1 Repeated dose (90-days) toxicity testing

Repeated dose (90-day) studies should be conducted in a rodent and a non-rodent species, the main objectives are to: identify target organs and toxicological endpoints; provide information to determine dose levels for chronic studies; identify the most appropriate species for chronic studies, and, identify a NOEL.

Further information is given in VICH Guideline 31: Safety Studies for Veterinary Drug Residues in Human Food: Repeat Dose (90-days) Toxicity Testing. Studies should be conducted in accordance with OECD Guidelines 408 (rodent) and 409 (non-rodent).

3.2.2 Repeated dose (Chronic) toxicity testing

Chronic toxicity testing should be conducted, unless demonstrated to not be necessary, in at least one species. This should be the most appropriate species chosen on the basis of all available scientific data, including the results of the 90-day studies. The default species is the rat. Further information is given in VICH Guideline 37, Safety: Repeat-Dose (Chronic) Toxicity Testing. The study should be conducted in accordance with OECD Guideline 452 (Chronic Toxicity Studies). Gross necropsy and histopathological examinations should be performed in accordance with details in the OECD 90-day toxicity study guidelines 408 (rodents) and 409 (non-rodents).

3.3 Tolerance in the target species

Tolerance studies are fundamental to the assessment of target species safety, but they are generally not relevant to the identification of ADIs for veterinary medicinal substances. Nevertheless, they may provide some data of relevance to the assessment of consumer safety. As such, the existing reports of tolerance studies should be provided as part of the Safety File.

3.4 Reproductive toxicity including developmental effects

Pharmacologically active substances can adversely influence reproductive performance of exposed adults as well as the normal development of their progeny. Tests for effects on reproduction are carried out with the objective to discover potential effects on male and female reproductive performance, such as gonadal function, oestrus cycle, mating behaviour, conception, parturition, lactation, weaning and on the growth and development of the offspring. These studies may also provide information about adverse developmental effects such as teratogenesis and serve as a guide for subsequent tests.

3.4.1. Study of the effects on reproduction

The aim of the study is to detect toxic effects on fertility in males and females and on other reproductive functions. Such data should usually be provided by a two-generation study in at least one species, usually a rodent. The oral route of administration should be used. The drug under study is administered to males and females for an appropriate time prior to mating.

Males should be dosed during growth and for at least one spermatogenic cycle; females should be dosed for at least two oestrus cycles. Administration is continued until weaning of the F2-generation. Each test group should yield a sufficient number of pregnant females at or near term. This is necessary to assure a meaningful evaluation of the potential of the substance to affect:

- Fertility, pregnancy and maternal behaviour;
- The suckling, growth and development of the F1-offspring from conception to maturity;
- The development of their offspring (F2) to weaning.

As a consequence of effects on the developing central nervous system, behavioural effects may arise. Specific investigation of such effects may be required where justified, for example by the results of other tests (see 4.2, neurotoxicity).

It may be necessary to perform studies in which treatment is restricted to either males or females, in order to determine whether an observed effect relates to one or both sexes.

Additional information is available in CVMP-VICH Guideline 22; Safety Studies for Veterinary Drug Residues in Human Food: Reproduction Studies. Advice on the conduct of two-generation reproduction studies is available in OECD Test Guideline 416.

3.4.2 Study of developmental toxicity including teratogenicity

The objective of this study/studies is to detect any adverse effects on the pregnant female and the development of the embryo and fetus as a result of exposure from implantation through the entire gestation period. Such effects include enhanced toxicity in the pregnant females, embryo-fetal death, altered fetal growth and structural abnormalities and anomalies in the fetus.

The CVMP-VICH Guideline 32 (Safety Studies for Veterinary Drug Residues in Human Food: Developmental Toxicity Testing) recommends a tiered approach. This starts with testing in the rat. If a negative or an equivocal result for teratogenicity is observed, another developmental toxicity study should be conducted in a second species, preferably the rabbit. If the rat study is positive for teratogenicity, a study in a second species is not necessary except where a review of all the core studies indicates that the ADI would be based on the rat teratogenicity. In this case a study in a second species would be required to determine the most sensitive species for this endpoint. Advice on the conduct of developmental toxicity studies is available in OECD Test Guideline 414.

3.5 Mutagenicity

A battery of tests is used to identify substances that may cause mutagenicity or genotoxicity. Substances that are considered to be genotoxic are regarded as potential carcinogens. Those that cause genetic damage in germ cells also have the potential to cause reproductive/developmental effects.

The mutagenicity of a drug is its ability to cause transmittable changes in the genetic material of cells. Mutations may be transmitted to the progeny through germ cells (germ cell or heritable mutation) or may be transmitted from one cell generation to another within the individuals (somatic mutation). Germ cell mutations result in many genetic diseases. Somatic mutation may be considered to be one cause of cancer and some other diseases. Such effects may occur as the results of changes:

- In the composition or arrangement of genes (gene mutation);
- In the structure and the number of chromosomes (chromosomal mutations, genome mutations).

Clues to the potential genotoxicity of a substance are given by its chemical structure. Certain moieties (structural alerts) are associated with the potential to react with DNA. The presence of such structural alerts in the molecular structure of a substance gives qualitative information that the substance may be genotoxic. All substances should be tested for mutagenicity in experimental systems, irrespectively of whether they possess structural alerts. However, the degree of experimental evidence needed to prove the

absence of genotoxicity of a substance with structural alerts may be greater than in the case of a substance having no structural alerts.

The objective of mutagenicity testing is to identify chemicals with such properties. In designing a mutagenicity testing procedure, the following points are of prime importance:

- The procedure should be able to identify mutagens with maximum accuracy;
- The procedure should be capable of detecting the entire spectrum of mutagenic events, notably gene mutations, chromosome mutations (clastogenicity) and genome mutations (e.g. aneuploidy).

CVMP-VICH Guideline (Guideline 23, Safety Studies for Veterinary Drug Residues in Human Food: Genotoxicity studies) recommends a standard battery of tests that can be used to evaluate the genotoxicity of veterinary drug residues. In most cases the results will give a clear indication of whether or not the test substance is genotoxic. However, the standard battery may not be appropriate for certain classes of drugs. For example, some antimicrobial substances may be toxic to the tester strains used in the bacterial gene mutation test, and additional testing may be required in some cases such as substances showing potential for aneugenic and/or germ cell effects.

The standard battery consists of the following three tests;

- A test for gene mutation in bacteria. This should be a bacterial reverse mutation test conducted in accordance with OECD Guideline 471. In the case of antimicrobials that are excessively toxic to the tester strains, the bacterial test should be conducted at concentrations up to the limit of cytotoxicity and supplemented with an *in vitro* test for gene mutation in mammalian cells in accordance with OECD guideline 476.
- An *in vitro* test for chromosomal effects in mammalian cells. In the EU, a chromosomal aberration test in accordance with OECD Guideline 473 is preferred. If there are indications of aneugenicity (e.g. hyperploidy/polyploidy), this should be confirmed using appropriate methods such as FISH (fluorescence *in situ* hybridisation) or chromosome painting.
- An *in vivo* test for chromosomal effects in required. This can either be a mammalian erythrocyte micronucleus test in accordance with OECD Guideline 474 using bone marrow (rat or mouse) or peripheral blood (mouse only), or a mammalian bone marrow chromosome aberration test following OECD Guideline 475.

The interpretation of the results of the standard battery of tests and the need for further testing should be considered in the light of the guidance given in the VICH Guideline.

For most genotoxicity endpoints, reliable methods do not exist to permit the identification of a threshold dose below, which there are no adverse effects. Aneuploidy is an exception to this, as a threshold concentration for tissue exposure may be identified.

3.6 Carcinogenicity

The aim of carcinogenicity bioassays is to determine the carcinogenic potential of substances. Carcinogenicity bioassays in laboratory animals represent the most suitable experimental approach to explore the carcinogenic potential of a substance. If appropriate, the study of carcinogenicity may be combined with long-term toxicity studies.

The harmonised CVMP-VICH guidelines require that carcinogenicity bioassays are necessary for substances that are suspected to have carcinogenic potential as elaborated in CVMP-VICH Guidelines 33 (General approach to testing) and 28 (Carcinogenicity testing).

3.6.1. Criteria for the selection of substances for carcinogenicity testing

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.

3.6.2. Carcinogenicity tests

Where carcinogenicity studies are required, they should normally consist of a two-year rat study and an 18-month mouse study, conducted in accordance with OECD guideline 451 (combined chronic toxicity/carcinogenicity studies in accordance with OECD guideline 453 would also be acceptable). With appropriate scientific justification, a study in a single species, preferably the rat, is acceptable. A positive response in either species is considered indicative of carcinogenic potential.

Testing should normally be conducted using at least three dose levels. Dosing should be via the oral route (preferably in feed). Further methodological advice is given in CVMP-VICH Guideline 28 and OECD Guidelines 451 and 453.

The results should be analysed by appropriate statistical methods. The particular tests used in the analysis of carcinogenicity studies, are intentionally not specified.

The criteria on which a substance may be defined as carcinogenic in evaluating the results of chronic bioassays are:

- An increase in the incidence of tumours as compared with the untreated control animals;

- An increase in the incidence of tumours as compared with historical control data;
- The development of tumours earlier than in the control animals;
- The occurrence of types of tumours usually not seen in untreated control animals.

If positive results for carcinogenicity are obtained, further studies may be considered to attempt to define the mechanism of tumour formation, in so far as this is possible. Some non-genotoxic mechanisms of carcinogenicity in laboratory animals may not be relevant to humans. Other non-genotoxic mechanisms may only come into play at high doses. If a non-genotoxic mechanism underlying the carcinogenicity (e.g. changes in serum hormone levels for a hormonally mediated cancer) and a NOEL can be clearly identified, this can be taken into consideration when establishing an ADI. Where a mechanism has not been identified for the carcinogenesis of a clearly non-genotoxic substance, it may be possible to use the NOEL for tumour production in the calculation of the ADI, providing that a suitably large uncertainty factor is used.

Negative results from carcinogenicity bioassays may not, on their own, be sufficient to demonstrate the safety of an *in vivo* mutagen. Substances or metabolites that cause genotoxicity *in vivo* are not permitted for use in veterinary medicines intended for food-producing animals due to the uncertainty in establishing a threshold for this effect.

4. Other effects

These tests are required to address safety concerns such as those based on compound structure, class and mode of action. Some examples of these studies are:

4.1 Immunotoxicity

Veterinary drug residues may cause adverse effects by interacting either directly or indirectly with the immune system. Inadvertent modulations or modifications of the immune system may be the basis for health effects, such as depression or enhancement of normal immune responses as well as the stimulation of allergic or hypersensitivity phenomena.

The applicant should supply details of all immunological studies that may have been performed as part of any aspect of the assessment of the substance (e.g. sensitisation assays performed for user safety or efficacy studies performed on immunomodulatory substances). Any reports of adverse effects in humans should also be provided.

If toxicological manifestations in experimental animals during repeated dose studies include specific changes in lymphoid organ weights and/or histology and changes in cellularity of lymphoid tissues, bone marrow or peripheral leukocytes, additional functional testing may be required. The investigator shall justify the nature and extent of the additional studies.

4.2 Neurotoxicity, developmental neurotoxicity and delayed neurotoxicity

Neurotoxicity testing will be required for substances belonging to the following classes of substances that are known to be associated with neurotoxicity: organophosphates, pyrethroids, carbamates and avermectins. Substances that are shown in other toxicological assays to cause histological, biophysical or biochemical changes to the nervous system should also be tested for neurotoxicity using the oral route. OECD Test Guideline 424 advises on the methodology to be used in neurotoxicity studies in rodents. The testing of organophosphates and carbamates should identify NO (A) ELs for inhibition of brain, erythrocyte and plasma/whole blood acetylcholinesterases. Although the latter endpoints are generally accepted as indicators of exposure, rather than overt toxicity, they are usually used to determine the overall ADI for organophosphates and carbamates in the absence of more sensitive endpoints. For some substances (e.g. pyrethroids) behavioural or functional changes may be the most sensitive indicators of neurotoxicity. Selection of neurobehavioural studies will be on a case-by-case basis.

Developmental neurotoxicity testing may be considered necessary in certain circumstances such as if a substance has been shown to cause neuropathology or neurotoxicity in adults, or cause other types of toxicity, indicative of nervous system involvement at a developmental stage. A Guideline for developmental toxicity testing (No.426) is being produced by OECD.

Organophosphates should be tested for delayed neurotoxicity in a hen assay that incorporates measurement of neuropathy target esterase (NTE) in brain tissue. Both single exposure (OECD Test Guideline 418) and repeated exposure (OECD Test Guideline 419) should be considered. Substances that can cause delayed neurotoxicity are not permitted for use in veterinary medicines intended for food-producing animals due to the uncertainty in establishing a threshold for this effect.

4.3 Microbiological properties of residues

The safety evaluation of antibiotic residues has to take into consideration the specific risk linked to their antimicrobial activity as well as their pharmacological properties. Antimicrobial activity may become the determining factor for safety evaluation when the toxicity of the substances under consideration is so low that high levels of residues could be accepted on the basis of the toxicological data.

4.3.1. Potential effects on the human gut flora

The question to be resolved is whether the ingestion of residues of antimicrobial agents in food of animal origin poses a risk to human health by disruption of the colonisation barrier function of the normal intestinal flora, or by increasing the population of resistant bacteria either due to acquisition of resistance by previously sensitive or to a relative increase in the proportion of less sensitive organisms.

These risks that result from residues, must be clearly distinguished from the potential risk to public health associated with the ingestion of food of animal origin which contains resistant bacteria selected under the pressure of an antimicrobial therapy.

The VICH guideline 36 (CVMP/VICH/467/03) implemented in May 2005 in the European Union, outlines the steps in determining the need for establishing a microbiological ADI. They recommend test systems for determining no-observable adverse effect levels/concentrations, including both *in vitro* and *in vivo* test systems. They also recommend procedures to derive a microbiological ADI.

4.3.2. Potential effects on the micro - organisms used for industrial food processing

The inhibitory effects of antibiotic residues on the manufacture of dairy products, such as yoghurt and cheeses are well known.

A CVMP Note for guidance for the assessment of the effect of antimicrobial substances on dairy starter cultures advises on the testing required to identify an upper limit concentration of an antimicrobial substance that will not adversely affect microbially mediated processing of dairy foods (EMEA/CVMP/276/99-FINAL).

4.4 Observations in humans

Studies in man are not normally requested, but the applicant should supply all available data on health effects in humans who were intentionally (e.g. use in human medicine) or unintentionally (e.g. occupational exposure) exposed to the substance. All epidemiological, pharmacological, toxicological or clinical data relevant for the evaluation of the substance under investigation should be provided.

5. Safety evaluation of residues

5.1 Proposal for an acceptable daily intake (ADI)

A summary of the relevant data of the pharmacological-toxicological testing is required. Then, the results of the toxicity studies in animals should be extrapolated to man and an ADI or alternative limit should be derived.

As indicated in the introduction to this volume, the ADI is an estimate of the amount of a substance, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk.

When pharmacodynamic or toxicological effects are the critical endpoints, the ADI should be based on the NOEL, which leads to the lowest ADI after appropriate uncertainty factors have been applied. The choice of the NOEL and the uncertainty factor should be justified. Occasionally, when only a minor

response is observed at the lowest dose used in a study, it may be possible to use a lowest observed effect level (LOEL) in place of a NOEL When the proposed ADI is based on microbiological effects, the method by which the ADI is derived should be clearly justified in accordance with the relevant CVMP/VICH guideline.

The overall ADI should be established on the lowest of the pharmacological, toxicological or microbiological ADI that has been determined for the substance.

Due to uncertainties in the extrapolation from experimental studies to human health effects, a numerical uncertainty factor is used to provide reassurance that the potential risk is not underestimated. It is usually assumed that human beings may be up to 10 times more sensitive than the test animal species and that the difference in sensitivity within the human population is a tenfold range. Therefore, where adequate studies are available, an uncertainty factor of 100 will usually be applied, although this may be increased or reduced, according to the data available.

Where the results of animal studies indicate teratogenic effects at doses, which do not cause maternal toxicity, an uncertainty factor of up to 1000 will be applied to the NOEL for teratogenicity. For non-genotoxic threshold carcinogens an uncertainty factor of up to 1000 may be used depending on the mechanism involved.

It may occur that the most sensitive endpoint is observed in a species and/or study where all dose groups produce significant effects compare to the control group. If the effect observed in the lowest dose in a sufficiently minor response, it may be possible to establish an ADI based on this LO(A)EL. In this case an additional uncertainty factor of 2 to 5 will be used to take into account that the LO(A)EL reference point is an unknown distance above the “true” threshold.

Where the ADI is to be set on the basis of human data, there is no uncertainty factor to be applied for extrapolation from animal to man. Thus, for good quality human data, it is appropriate to apply an uncertainty factor of 10 to account for variation in individual response between human beings. The existence of human data does not justify any reduction in the uncertainty factors applied to NOELs derived from animal studies.

Other methods of identifying uncertainty factors (e.g. IPCS, 1999, “Principles for the assessment of risks to human health from exposure to chemicals” EHC 210) would be acceptable in place of the usual standard factors if adequate justification was provided.

Having regard to the previous considerations, the uncertainty factor proposed by the applicant will usually have a value between 10 and 1000. Other values may be considered give appropriate justification.

The formula used to determine the ADI is as follows:

$$ADI = \frac{\text{NOEL (mg/kg bw/day)}}{}$$

Uncertainty Factor

(mg/kg bw)

The methodologies for establishing a microbiological ADI for substances with antimicrobial activity are detailed in the VICH guideline 36 (CVMP/VICH/467/03).

The NOEL-uncertainty factor approach is not applicable to non-threshold effects. Substances that can cause genotoxic carcinogenicity or delayed neurotoxicity are not permitted for use in veterinary medicines intended for food-producing animals due to the uncertainty in establishing a threshold for these effects.

5.2 Alternative limits

In the case of other endpoints where there may be uncertainty regarding the threshold for the effect (e.g.such as allergenicity) an alternative approach to the safety evaluation of residues may be required, taking into account the assessment of the overall risk to the health of consumers from the substance as a whole.

B. Residue File

I. General considerations

The determination of MRLs for a pharmacologically active substance has two goals:

- to provide values for the establishment of withdrawal periods when applications for marketing authorisations are submitted for specific veterinary products,
- to provide a reference point for control of residues in edible tissues or products from treated food producing animals.

As mentioned previously, the CVMP has developed a number of further guidance documents in the form of guidelines, notes for guidance or position papers where specific problems need to be addressed.

These documents outline how specific problems (data requirements for minor species, MRLs for species of fish, selection of target tissues, etc.) should be addressed and what else needs to be taken into consideration when compiling a dossier in support of an application for establishment of MRLs.

The current versions of such guidance documents are listed at the end of this volume and are available on the EMEA website (http://www.emea.eu.int).

1. Proposals for Maximum Residue Limits (MRLs)

Starting from the acceptable daily intake (ADI) or alternative limit deduced from the studies compiled in the safety file, the maximum residue limits (MRLs) should be established for each edible tissue of each target species for which the pharmacologically active substance is intended.

When proposing MRLs, applicants must ensure that the ADI is not exceeded after considering intake from all sources. In particular, when substances are also used as plant protection products (i.e. pesticides) the ADI should be divided, the part generally reserved for the veterinary use being 45%. This partition was based on the partition of the total human food basket into food of animal origin and food of vegetable origin. It may not be possible to use this value if the portion of the ADI used by an existing pesticidal authorisation exceeds 55%. On the other hand, where the existing pesticidal authorisation allows and sufficient data are available on intake from pesticidal uses, it may be possible to allocate a larger part to veterinary uses without exceeding the ADI.

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 uncertainty 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 is

considered as the default approach. The basis and considerations for those extrapolations are detailed 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)

A complete set of data should be provided for major species whereas a limited package of data should be sufficient for a substance used only in minor species as further explained in the corresponding CVMP Note for Guidance on the Establishment of Maximum Residue Limits for Minor Animal Species (EMEA/CVMP/153a/97-FINAL) – *currently under revision.*

1.1 Establishment of MRLs in edible tissues

For mammals, the edible tissues are muscle, liver, kidney, fat (or for pigs, fat and skin in natural proportions). For poultry, the edible tissues are muscle, liver, kidney, fat and skin in natural proportions. For fish, the edible products are muscle and skin in natural proportions.

As a general rule, where residue concentrations can be quantified in the edible tissues MRLs should be established for all edible tissues based on the tissue residue distribution pattern of the pharmacologically active substance investigated.

1.2 Establishment of MRLs in other products (milk, eggs and honey)

Residues studies should be conducted in milk, eggs and honey.

MRLs in milk, eggs and honey are only established further to applications supported by the required data.

List of edible tissues and products:

Mammals	**Poultry**	**Fish**	**Bees**
Muscle	Muscle	Muscle and skin in natural proportions.	Honey
Liver	Liver		
Kidney	Kidney		
Fat, or fat and skin in natural proportions (pigs)	Fat and skin in natural proportions		
Milk	Eggs		

1.3 Proposed MRLs

The proposed MRLs should be given in the following format:

1. Substance for which MRLs are proposed;
2. List of commodities and proposed MRLs:
    a. Commodity;
    b. MRL (µg/kg);
    c. Definition of the marker residue on which the MRL is proposed to be established.

2. Basis to determine MRLs

It is important to recognise that there is no simple equation, which can be used to determine the MRLs. The determination of MRLs is settled on several key points:

- Statement of the deduced acceptable daily intake or alternative limit;
- Basis for the calculations: arbitrary body weight of the consumer and consumption figures;
- Proposal of marker residue;
- Ratio of marker residue with regard to the total residues;
- Tissue distribution;
- MRLs and calculation of the amount of residues susceptible to be ingested.

2.1 Statement of the deduced acceptable daily intake or alternative limit

A short summary of relevant data of the pharmacological-toxicological testing is required, followed by a description of the necessary extrapolations to man and the calculations of an acceptable daily intake (ADI) or alternative limit.

2.2 Basis for the calculations: arbitrary body weight of the consumer and consumption figures

Since the ADI is related to bodyweight, an human body weight of 60 kg has been defined to estimate the maximum acceptable residue daily intake to be ingested by the consumer (ADI (µg/kg) x 60 kg).

The MRLs for residues in various edible tissues and products are, in addition, a function of the amount of food items consumed. Therefore, consideration should also be given to consumption levels of tissues, organs and animal products representing significant constituents of the total daily diet (e.g. meat (muscle), edible offal (liver, kidney), eggs, milk, any other raw material used for processed meat products). Individual food preferences are highly variable. Since data based on scientifically reliable intake surveys are difficult, if not impossible, to come by, the following high arbitrary daily consumption should be applied in order to assure protection of consumers:

Food basket

Mammals		**Poultry**		**Fish**		**Bees**	
Muscle	0.300 kg	Muscle	0.300 kg	Muscle and skin in natural proportions	0.300 kg	Honey	0.020 kg
Fat	0.050 kg (1)	Fat and skin in natural proportions	0.090 kg				
Liver	0.100 kg	Liver	0.100 kg				
Kidney	0.050 kg	Kidney	0.010 kg				
Milk	1.500 kg	Eggs	0.100 kg				

(1) Fat and skin in natural proportions for pigs

2.3 Proposal of marker residue(s)

2.3.1 Marker residue

From the results of the depletion studies in edible tissues, a marker residue is defined. The marker residue is the parent drug or any of its metabolites or a combination of any of these with a known relationship to the concentration of the total residue in each of the various edible tissues atthe expected withdrawal time. In this case, the MRLs establish the concentration of marker residue permitted in the target tissues.

Marker residue and target tissues are selected in such ways that total residues in each edible tissue are at or below its safe concentration if the marker residue is at or below the MRLs.

For milk or eggs, it may be necessary to select a marker residue that is different from the marker residue selected for the target tissue representing the edible carcass.

2.3.2. Ratio Marker residue/total residues

The ratios of the marker residue/total residues in connection with the ADI (i.e. ratio of marker residue/total radioactive residues, marker residue/all microbiologically active residues, marker residue/all pharmacologically active residues) must be defined. In particular, this ratio should be determined at the expected withdrawal time chosen in such a way that the total residues to be ingested in the food basket are below the ADI.

In accordance with the CVMP note for guidance (EMEA/CVMP/153b/97), the parent compound is normally acceptable as a valid marker residue in *Salmonidae* and other in fish.

2.4 Distribution in edible tissues

The individual MRLs in each edible tissue should, reflect the kinetics of the depletion of the residues leading to set MRL figures proportionally to the marker residue concentrations.

The CVMP position paper EMEA/CVMP/029/97 - Selection of target tissues for the establishment of MRLs under Council Regulation (EEC) No 2377/90, states that: For mammals and poultry, if residue levels cannot be quantified in one or two of the four edible tissues, MRLs should be established for the tissues where the concentrations are sufficient, but in any case for one of the edible tissues of the carcass (muscle or fat) and one of the edible tissues of the offal (liver or kidney). The MRLs established allow for monitoring of residues. Major edible tissues that are identified as not relevant for monitoring purposes (non-target tissues) will be stated and the reasons given in the summary report.

In those rare cases where both muscle and fat residues are below the limit of quantification, but where an MRL is necessary for surveillance purposes, an arbitrary limit at the limit of quantification of the analytical method for one of these tissues is necessary. Here again, this fact should be stated in the summary report.

2.5 Consideration of other factors that influence the establishment of MRLs

Information on the following key points is necessary to establish MRLs:

- The ADI or an alternative limit;
- The marker residue must be clearly defined;
- The slaughtering point where the marker residue can be measured in sufficient concentration to establish a tissue distribution must be clearly indicated;
- The figures corresponding to the ratio of the marker residue towards total residue should be calculated for each edible tissue and product (further guidance of the CVMP to be considered where appropriate);
- For milk, the MRLs should not exceed the concentration without effect on dairy starter cultures;
- In addition, when a substance is also used as pesticide, it should be kept in mind that the definition of the edible tissues for the establishment of MRLs differs. For pesticide use, the target tissues are meat (including intermuscular fat and subcutaneous fat), offal and milk. Where MRLs have already been established for pesticide use, the MRL established for veterinary use would correspond to the MRL established for pesticide use for meat/offal with low fat content (less than 10%);
- It should be considered whether some of the ADI needs to be retained for proposals for MRLs of the substance in milk, eggs and honey.

All these parameters must be taken into account for proposals for MRLs. However, for all cases MRLs should be proposed in such a way that the total amount of residues likely to be ingested does not exceed the ADI or alternative limit.

In those rare cases where both muscle and fat residues are below the limit of quantification, but where an MRL is necessary for surveillance purposes, an arbitrary limit at the limit of quantification of the analytical method for one of these tissues is necessary.

If a substance could be applied to several or all-relevant species of food-producing animals, it is imperative to check that the total amount of residues ingested:

0.500 kg meat of mammals or poultry or 0.300 kg fish

Plus 1.500 kg milk

Plus 0.100 kg eggs

Plus 0.020 kg honey

Remains below the ADI or an alternative limit as follows:

Edible tissue or products	**Daily consumption (kg)**	**MRL proposal (µg/kg)**	**Ratio of the marker/total residue**	**Amount per edible tissue or product**
Muscle	0.30	M1	R1	(M1 • 0.3)/R1
Fat				
Mammals	0.05*	M2	R2	(M2 • 0.05)/R2
Poultry	0.09**			(M2 • 0.09)/R2
Liver	0.10	M3	R3	(M3 • 0.10)/R3
Kidney				
Mammals	0.05	M4	R4	(M4 • 0.05)/R4
Poultry	0.01			(M4 • 0.01)/R4
Milk	1.50	M5	R5	(M5 • 1.50)/R5
Eggs	0.10	M6	R6	(M6 • 0.10)/R6
Honey	0.02	M7	R7	(M7 • 0.02)/R7

ADI (µg per person)	*Statement of the value of the relevant ADI*
% Total used for veterinary products	$\frac{\text{Sum of relevant fields of the last column of the above table}}{\text{ADI}} \cdot 100$
% ADI used for pesticide products	$\frac{\text{Sum of relevant MRLs for pesticidal use}}{\text{ADI}} \cdot 100$
Total [veterinary + pesticide use]	Sum of the 2 above fields

* fat and skin in natural proportion for pigs ** fat and skin in natural proportion

The applicant should consider available MRLs set by other scientific organisations including Codex Alimentarius, JECFA and JMPR. Applicants should always consider the feasibility of proposing MRLs substantially below those derived from the ADI, having regard to the conditions of use proposed for the

veterinary medicinal product, the need to ensure practical withdrawal periods. For each major species, if the concept of distribution is correctly followed, the MRLs proposed for the edible tissues (muscle, fat, liver and kidney) should lead to similar withdrawal periods for each edible tissue.

2. Objectives of MRLs

3.1 Proposal of target tissues

The target tissue is the edible tissue selected to monitor for the total residue in the target animal. The target tissue is usually, but not necessarily, the tissue with the slowest depletion rate of the residues.

When a substance 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.

When a substance is to be used in bees, honey will be the target tissue.

3.2 Impact on the determination of Withdrawal Periods

The withdrawal period is defined in Point 9 of Article 1 of Directive 2001/82/EC, as amended[17]:

"*The period necessary between the last administration of the veterinary medicinal product to animals, under normal conditions of use and in accordance with the provisions of this Directive, and the production of foodstuffs from such animals, in order to protect public health by ensuring that such foodstuffs do not contain residues in quantities in excess of the maximum residue limits laid down pursuant to Regulation (EEC) No 2377/90*".

The withdrawal period should provide a high degree of assurance both to the producers and the consumers that the concentrations of residues in foods derived from treated animals are not above the permitted concentrations.

The withdrawal periods for animal slaughter as well as for the production of milk, eggs and honey for human consumption are determined from the results of suitable residue depletion studies using the formulation intended for marketing.

Thus, MRLs have an impact on withdrawal periods. Withdrawal periods are however set in the context of granting marketing authorisations for veterinary medicinal products. The CVMP has issued further guidance on the setting of withdrawal periods.

Normally, an MRL established for muscle will also be applicable to muscle at the injection site for those substances administered by the intramuscular or subcutaneous routes. The CVMP has published specific updated guidance on this subject. The CVMP Guideline on injection sites (EMEA/CVMP/542/03-FINAL) is available on the EMEA website (http://www.emea.eu.int).

[17] OJ L136, 30.04.2004, p 58-84, coming into force by 30 October 2005.

4. Regulatory analytical method

Applicants should always make available a validated analytical method, which can serve as a basis for official residue monitoring and surveillance ("regulatory method") for all the tissues for which MRLs have been set. This method should determine the marker residue on which the MRLs are based.

5. Extrapolation of MRLs

The approach for the extrapolation of existing MRLs to other species, which was already foreseen for minor animal species and described in the CVMP Note for Guidance on the Establishment of Maximum Residue Limits for Minor Animal Species (EMEA/CVMP/153a/97-FINAL) – *currently under revision* and for *Salmonidae* and other fin fish in the Note for Guidance on the Establishment of Maximum Residue Limits for S*almonidae* and other Fin Fish (EMEA/CVMP/153b/97-FINAL), was further developed in light of experience gained and is detailed in the 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 latter guidance advises on the approach for extrapolations of MRLs as follows:

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 Establishment of Maximum Residue Limits for Minor Animal Species (EMEA/CVMP/153a/97-FINAL) –***currently under revision*** and in the Note for Guidance on the Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of Animal Origin (EMEA/CVMP/187/00-FINAL).

6. Annex II

In accordance with Article 3 of Council Regulation (EEC) No 2377/90, as amended, "*where* […] *it appears that it is not necessary for the protection of human health to establish a maximum residue limit"* pharmacological active substances can be inserted in Annex II.

It may be possible to justify entry of a substance into Annex II of Regulation (EEC) No 2377/90, even in the absence of an established ADI or alternative safety limit, if the quality of the full package of data is sufficient to ensure that there is no risk to human health. For instance, Annex II entry might be acceptable if it can be demonstrated that use of the substance in food-producing animals would not result in detectable residues in food derived from the treated animals. This would not apply to genotoxic carcinogens, which are assumed to be harmful at any level of exposure (even below the detection limit). An Annex II may be accompanied by specific restrictions on use, such as a particular route of administration.

The CVMP has identified a number of criteria for inclusion of substances into Annex II of Regulation (EEC) No 2377/90 in the Note for Guidance on the risk analysis approach for residues of veterinary medicinal products in food of animal origin (EMEA/CVMP/187/00-FINAL).

6.1 Criteria for inclusion into Annex II

1. 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

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

6.2 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 Applicant .
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.

II. Specific requirements

1. Precise identification of the substance and the product concerned by the application

The substance or product, which is the subject of the application, should be clearly and specifically identified in accordance with the requirements laid down in Regulation (EEC) No 2377/90 and/or Directive 2001/82/EC.

Adequate specifications should exist for the substance (product) being tested, including purity (limits of impurities), particle size, solubility and any other factors, which may influence its activity. Each batch used in the tests should be identified. Whenever possible, the test substances should have the same pattern of impurities as the product to be marketed. Should the final dosage form have significantly different impurities, further investigation will be required.

2. Residue studies

2.1 Pharmacokinetics

With respect to consumer safety, the aim of the pharmacokinetic studies is to evaluate the absorption, distribution, metabolism and excretion of the product in the target species. Data should demonstrate the time course of the concentrations of the parent drug and/or its metabolite(s) in tissues and body fluids. The study is normally carried out in healthy animals. If diseased animals are used this should be indicated.

2.1.1. Absorption

The absorption of the substance concerned should be documented. Depending on the route of administration of any substance, the following parameters should be studied, if applicable:

- Following oral administration, absorption by the animal, effects caused by species differences in digestive physiology and sites of metabolism (e.g. first pass effects);
- Absorption following topical application;
- Release from injection sites;
- Systemic availability following other specific routes (intra-mammary application, intra-uterine administration etc.).

In the case of substances or products administered by the oral or dermal routes, where it is proven that systemic uptake is negligible, then further residue studies are not required. However, if there is significant systemic uptake, full residue studies are required.

2.1.2. Distribution

The distribution should be described by the following pharmacokinetic parameters.

- Volume of distribution,
- Tissue and blood/plasma ratios,
- Influences of animal physiology on distribution,
- Plasma protein binding,
- Accumulation after repeated administration.

2.1.3. Metabolism

Different biotransformation products may possess different toxic potentials. Therefore, information on the chemical nature, the concentration, and the persistence of the total residue is required. The purpose of the metabolism study in the target species is to provide the necessary information on the metabolic fate of the drug in the edible tissues

These studies are also necessary in order to check whether the metabolite(s) found in target animals are the same as those found in the laboratory animals used for toxicity testing.

All the available data from any application in the target species, the test species (including *in vitro* systems) and, as far as available, data from human use should be considered. The studies should provide the following types of information for an adequate evaluation of the metabolism of the product:

- Nature of the metabolite(s):
    - Chemical nature of residues in edible tissues (muscle, liver, kidney, fat) and in products (milk, eggs and honey);
    - Influence of the route of administration on the metabolic profile ;
    - Relationship between structure and biological activities, if available.
- Bioavailability of bound metabolite(s), characterisation of the type of binding of biologically relevant drug metabolite(s) to constituents of edible tissues.

2.1.4. Excretion

Data on the elimination in target species are requested. These should include the principle routes of elimination; renal excretion (including effects on excretion, availability for filtration (plasma protein binding), pH of the urine); faecal elimination. All other routes of excretion should be considered when appropriate (milk, expired-air, etc)

2.1.5. Depletion of residues

The applicant should measure the depletion of total drug-related residue in edible tissues of target animals after the last administration of the drug.

Radiotracer methodology is currently the most useful technique for determining the total drug-related residue.

However, depending on the ADI established, alternatives may be used such as a microbiological method in order to measure the total microbiologically active residues

The total residue depletion study should be conducted with previously unmedicated animals that are representative of the proposed target populations. Animals of both sexes should be used if a product is intended for use in both female and male animals. After animals have been treated with the drug, edible tissues and biological fluids should be collected at appropriate times for residue analysis.

From these studies, the total amount of residues and the metabolite(s) in edible tissues or products may be measured in order to determine the ratio of the marker residue to total residues without extrapolation.

The results of the residue depletion studies should indicate whether and, if so, how long after the application of the veterinary medicinal product, residues occur in the foodstuffs obtained from treated target animals.

For an injectable product, the applicant should also measure the depletion of residue remaining at the injection site in accordance with the CVMP guideline (EMEA/CVMP/542/03-FINAL).

3. Performance of tests

All studies shall be conducted and reported in conformity with the principles of Good Laboratory Practice (GLP) and quality compliance recognised by specific Community legislation in Directives 87/18/EEC and 88/320/EEC and should follow available internationally recognised and regularly updated test protocols.

In addition, the following detailed information should be given if applicable:

- Species/strain/source of test animals used, sex of the dosed animals;
- Number, age and body weight;

The groups of animals used should be large enough to allow a meaningful assessment of the data. It is recommended that at least the following numbers of animals be sampled at each time-point:

For the establishment of MRLs:

- Large animals: 4 per slaughter time;
- Poultry: 6 per slaughter time;
- Fish: 10 per slaughter time;
- Lactating cattle for milk collection: 8 animals, including animals at second or subsequent lactations (4 high yielding animals at an early stage of lactation and 4 low yielding animals at a late stage of lactation);
- Laying birds for egg collection: sufficient to collect 10 eggs per time-point.

For the determination of withdrawal periods (all target species)[18]:

- A statistically valid number of animals, which adequately reflects the target population of animals, are needed (see further guidance on the determination of withdrawal periods issued by the CVMP);
- Conditions of animal husbandry; water and food consumption (especially for drugs administered in drinking water and/or feed);
- Formulation of the administered drug and method of dose preparation;
- Mode of dose administration (dose [expressed in mg/kg body weight], frequency of dosing, and duration of treatment).

The applicant must also conduct depletion studies with the formulation of the product, which should be as close to the final formulation intended to the target animals at the maximum dose. The results of the residue depletion studies should indicate whether and, if so, how long after the application of the veterinary medicinal product, residues occur in the foodstuffs obtained from treated target animals.

The administered drug should have a high radio-purity. The applicant should choose the site(s) or radio label to assure that portions of the parent drug that are likely to be of concern to consumer safety are adequately labelled. The stability must be checked. The specific activity of the drug should be high enough to demonstrate that the concentrations of the total residue at the last sacrifice time are below that proposed. The following information should be given:

- Chemical identity of test substance(s); purity of test substance(s);
- Stability, including stability in vehicle and feed when so administered;
- Specific activity and radio-purity of labelled substances.

[18] Refer to CVMP guidelines on determination of withdrawal periods for full details and animal numbers.

- Sample collection, sample size, and sample storage;
- Depending on the nature of the product under investigation, between 3 and 5 equally spaced time-points appropriately chosen will usually be required. Normal animal husbandry conditions should be followed;
- Sampling of milk and egg-production should be conducted over a time period sufficient to follow the depletion of the substance and its metabolite(s);
- Honey: 5 samples from each of 5 hives, the time points to consider should be defined according to the period of treatment and the production of honey;
- Analytical methods (a complete description of the procedure, including preparation of analytical samples, instrumentation and data derived from standards, control tissues, fortified tissues and incurred tissues; the analytical method should be validated for the following parameters: limit of detection, limit of quantification, linearity for a range of concentrations, stability, accuracy, precision and susceptibility to interferences;
- Raw data of all test results including those of the analytical method used to determine the residues in the edible tissues or products, methods of calculation;
- The results of the experiments should be presented in an appropriate form that facilitates their review;
- Summaries of data in tabular form.

Where applicable, all observed results should be evaluated by an appropriate statistical method and be discussed in conjunction with the other available studies.

4. Development and validation of a proposed regulatory analytical method

Commission Decision 2002/657/EC of 12 August 2002[19] lays down the reference methods and the list of national reference laboratories for detecting residues.

In view of the need for national reference laboratories to have appropriate methods of analysis to ensure that MRLs established by the Community are not exceeded, the Committee for Medicinal Products for Veterinary Use agreed that such MRLs should be at least twice the limit of quantification of such methods. Therefore, the analytical method, which has to be submitted as part of the application as required in Annex V to Regulation (EEC) No 2377/90, should be validated across a range which at least includes one-half and twice the MRL.

The applicant shall validate the proposed regulatory analytical method according to the following criteria: specificity, accuracy, precision, limit of detection, limit of quantification practicability and applicability under normal laboratory conditions.

[19] OJ L 221, 17.8.2002, p. 8.

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 fully validated analytical methods in place also for 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 (See Note for Guidance on the Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of animal Origin – EMEA/CVMP/187/00-FINAL).

For the adaptation of the analytical methods to the needs of the Community and National reference laboratories for the surveillance, any additional information that may be available concerning the method, such as alternate detection techniques or clean-up procedures or sample handling processes (such as e.g. appropriate solvents, choice of extraction procedure or reasoning for the development of a specific method), would be helpful to be included in the method description.

It would also be beneficial to the official laboratories in their work to adapt the methods provided in the MRL procedure, if a contact person of the applicant/marketing authorisation holder is identified, in case of questions and exchange of information. In order to facilitate a co-operation between the laboratory and the applicant, it is recommended that the applicant indicate with the submission of the analytical method in the MRL dossier a contact point for this purpose. It is also recommended that relevant updates in this respect be provided to the EMEA.

4.1 Description of the procedure

The method should be capable of determining the marker residue and should be described in an internationally recognised standard layout (e.g. ISO 78/2). The following information should be given:

- Purpose and scope;
- Reagents;
- Equipment;
- Collection of samples;
- Storage of samples;
- Preparation of the laboratory sample;
- Preparation and clean-up of tissue extracts;
- Procedure for the determination of the residues;
- Calculation of results (e.g. method of standardisation, use of calibration curves, mathematical model, parameters, working range);
- Quality control (internal).

4.2 Validation of the procedure; quantitative estimates of the performance characteristics of the proposed method

Applicants should develop methods that are robust. Any proposed method should, in addition, be characterised by a set of attributes as follows:

- Specificity;
- Accuracy;
- Precision (repeatability within laboratory);
- Limit of detection;
- Limit of quantification;
- Practicability and applicability under normal laboratory conditions;
- Susceptibility to interference;
- Stability of the analyte during the analysis.

For establishing the performance characteristics suitable test material should be used (e.g. reference materials or in the absence thereof, blank tissues, fortified tissues, or tissues from dosed animals containing biologically incurred total residue). Relevant raw data, worksheets, chromatograms, spectrograms, calculations, statistical analyses etc. should be submitted together with the results of the evaluation of the method according to the above criteria. These criteria should be clearly defined. The following definitions are proposed. Other definitions are acceptable, provided that the content of information obtained remains equivalent.

4.2.1. Specificity

Specificity is the ability of a method to distinguish between the analyte being measured and other substances, which may be present in the sample being analysed.

This characteristic is predominantly a function of the measuring principle used. Details concerning specificity must relate at least to any substances which are likely to be present and to give rise to a signal when the measuring principle described is used, e.g. homologues, analogues metabolic products of the residues of interest. From the details concerning specificity it must be possible to determine the extent to which the method can distinguish between the analyte and the other substances under the experimental conditions.

4.2.2. Accuracy

It is proposed to use the following definition of the accuracy of the mean: ”the closeness of agreement between the true value and the mean result, which would be obtained by applying the experimental procedure a very large number of times”. The principal limitations on accuracy are:

- Random errors (i.e. low recovery);
- Systematic errors.

The following recommendations should serve as general guidance. For the repeated analysis of a (reference) sample with an analyte content for each concentration tested, the deviation of the mean from the true value, should not lie outside the following limits:

Content (Mass fraction)	**Limits**
<1 µg/kg	-50% to +20%
> 1 µg/kg	-30% to +10%

Note 1: Trueness is normally expressed by the difference between the mean value measured for an analyte in a certified reference material and its certified value, expressed as a percentage of this value, this criterion could not be considered for MRL applications as no certified material is available. Therefore, in place of trueness, the systematic error is expressed in terms of recovery.

Note 2: The accuracy could be determined by recovery experiments using fortified blank matrices (mutually independent replicates). For example, 18 blank test portions could be selected and fortified 6 at each analyte level, which should encompass 0.5x and 2x the MRL.

4.2.3. Precision

Precision means the closeness of agreement between mutually independent test results. It covers repeatability and within-laboratory reproducibility.

Repeatability: The closeness of agreement between mutually independent test results obtained under repeatability conditions, i.e. with the same method on identical test material in the same laboratory by the same operator using the same equipment within short intervals of time (one batch analysis).

A useful measure of precision is the relative standard deviation or co-efficient of variation (co-efficient of variation: the ratio of the standard deviation to the absolute value of the arithmetic mean).

The following recommendations should serve as a general guidance. In the case of repeated analysis of a (reference) sample under repeatability conditions, the co-efficient of variation (CV%) should not exceed the following values:

Content (Mass fraction)	CV
< 1 µg/kg	35%
> 1 µg/kg and < 10 µg/kg	30%
> 10 µg/kg and < 100 µg/kg	20%
> 100 µg/kg	15%

For example, 3 test samples should be fortified at analyte levels, which should encompass 0.5x and 2x the MRL. Then, 6 test portions of each level should be taken**,** analysed and the residue concentration of each tes**t** portion should be determined. Then, at each fortification concentration, the CV should be calculated.

Within-laboratory reproducibility: This is the distribution of measurement results obtained under in-house reproducibility conditions, i.e. at the same laboratory and with the same method, specified test materials, preferably different operators, different environmental conditions (multiple batch analysis).

For analyses carried out under within-laboratory reproducibility conditions, the within-laboratory CV should not exceed the level calculated by the Horwitz equation.

The equation is:

$CV = 2^{(1 - 0.5 \log C)}$

Where C is the concentration of the analyte expressed as a decimal fraction (e.g. 1 µg/kg is inserted into the equation as 10^{-9}). Representative values at a range of concentrations are shown below:

Representative within laboratory CVs for quantitative methods at a range of analyte contents

Content (mass fraction)	Within laboratory CV (%)
100 µg/kg	<23
1000 µg/kg	<16

For concentrations lower than 100 µg/kg, the CVs should be as low as possible practicable without exceeding the CVs given by the Horwitz equation. This should be tested on a number of mutually exclusive occasions (e.g. n ≥ 3 separate days). The analyte concentration of each fortified sample should be determined as the arithmetic mean of the test portion analyses achieved on each occasion.

4.2.4. Limit of detection

The limit of detection is the smallest measured content of an analyte from which it is possible to deduce the presence of the analyte with reasonable statistical certainty. One possible way to estimate the limit of detection is as follows:

The limit of detection is determined as the arithmetic mean of the analyte concentrations determined using the analytical procedure, as proposed, in a representative number of mutually exclusive blank samples ($n \geq 20$) plus three times the standard deviation. Other methods of calculation providing substantially the same statistical certainty may be used.

4.2.5. Limit of quantification (or determination)

The limit of quantification corresponds to the smallest measured content of an analyte above which a determination of the analyte can be made with a specified degree of accuracy and precision.

In its "region of" quantification" (at and above the limit of quantification and over a range of analyte concentration suitable for the enforcement of the MRL) the method has to meet the above requirements of accuracy and precision.

The CVMP agreed the following for the ratio of the limit of quantification to the MRL (EMEA/CVMP/274/96-FINAL):

In view of the requirements of Commission Decision 93/257/EEC[20], Commission Decision 93/257/EEC, Council Directive 86/469/EEC[21], [22] as amended and [23], and in particular, the need for national reference laboratories to have appropriate methods of analysis to ensure that MRLs established by the Community are not exceeded, the Committee for Veterinary Medicinal Products agreed that such MRLs must significantly exceed the limit of quantification. Furthermore, the limit of quantification of the analytical method, which has to be submitted as part of the application as required in Annex V to Council Regulation (EEC) No 2377/90, must be validated at one-half the MRL.

The Committee agreed that, in some cases, where the development in scientific and technical knowledge would limit the implementation of this requirement, alternatives could be considered when duly justified by the applicant. Such cases should nevertheless remain exceptional as the Committee considered that in most cases the MRL would be high enough with regard to the limit of quantification of the analytical method to allow for the implementation of this requirement.

[20] OJ No L 118, 14.5.1993, p. 75
[21] OJ No L 275, 26.9.1986, p.36
[22] OJ No L 66, 10.3.1989, p.37
[23] OJ No L 66, 10.3.1989, p.37

4.2.6. Practicability and applicability under normal laboratory conditions

Practicability

Practicability is a non-standard characteristic of an analytical procedure. It is dependent on the scope of the method and is determined by requirements, such as availability of standards, reagents and equipment, sample through put and costs. The following minimal requirements should be met:

- The method utilises commercially available standards, reagents, and equipment;
- The method should be designed to be performed safely by trained analysts[24];
- It should be possible to complete a sufficiently large number of analyses within reasonable time-periods.

Applicability

Applicability refers to the commodities to which the method can be applied as described or with minor modifications. Depending on the application of the veterinary medicinal product, it may be necessary to require that the method should be applicable to the analysis of any commodity to which MRLs apply.

4.2.7. Susceptibility to interference

This relates to susceptibility to non-specific influences on the analytical results of certain experimental conditions. For all experimental conditions, which could in practice be subject to fluctuation (e.g. stability of reagents, composition of the sample, pH, temperature) any variation, which could affect the analytical results, should be indicated. The description of the method should include any foreseeable interference. If necessary, additional methods for confirmation should be described. It is of prime importance that any interference, which might arise from matrix components, should be investigated.

4.2.8. Stability of the analyte during the analysis

The stability of the substance

- In solvent during storage,
- In matrix during storage/sample preparation and
- In extract during storage/analysis

Should be tested.

[24] Whenever possible, the use of hazardous substances should be avoided

The performance criteria laid down in Commission Decisions laying down analytical methods to be used for detecting certain substances and residues thereof in live animals and animal products according to Council Directive 96/23/EC may be considered where appropriate.

DEFINITIONS

- **Acceptable daily intake (ADI):** the estimate of the residue, expressed in terms of micrograms or milligrams per kilogram of bodyweight, that can be ingested daily over a lifetime without any appreciable health risk.
- **Active substance:** Any substance with pharmacological activity (substance as defined in Directive 2001/82).
- **Daily food basket:** The standard type and amount of food of animal origin, which is consumed by a person on a daily basis.
- **Excipient:** Any substance added to a veterinary medicinal product to give suitable consistency or form to the product.
- **Marker residue:** A marker residue is that residue the concentration of which decreases in a known relationship to the concentration of total residues in tissues, eggs, milk or other animal tissues.
- **Maximum residue limits (MRLs):** the maximum concentration of residue resulting from the use of a veterinary medicinal product (expressed in mg/kg or μg/kg on a fresh weight basis) which may be accepted by the Community to be legally permitted or recognised as acceptable in or on a food.
- **Residues of veterinary medicinal products:** all pharmacologically, toxicologically or microbiologically active substances, whether active substances, excipients or degradation products, and their metabolites which remain in foodstuffs obtained from animals to which the veterinary medicinal product in question has been administered.
- **Target tissue**: the edible tissue selected to monitor for the marker residue (*q.v.*) in the target animal.
- **Toxicological activity/effects:** Any adverse changes (a change that is statistically and biologically significant) in the structure or function of a biological system as a result of exposure to a substance.
- **Veterinary medicinal product:** Any substance or combination of substances having properties for treating or preventing disease in animals. Any substance or combination of substances which may be used in or administered to animals with a view either to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis [EC].
- **Withdrawal period***:* the period necessary between the last administration of the veterinary medicinal product to animals, under normal conditions of use and in accordance with the provisions of Directive 2001/82/EC, and the production of foodstuffs from such animals, in order to protect public health by ensuring that such foodstuffs do not contain residues in quantities in excess of the maximum residue limits laid down.

Guidelines relating to the establishment of MRLs

EMEA/CVMP/036/95 – Note for Guidance: Approach towards Harmonisation of Withdrawal Periods for Meat (CVMP adopted April 1996).

EMEA/CVMP/153a/97 – Note for Guidance on the Establishment of Maximum Residue Limits for Minor Animal Species (CVMP adopted 12 November 1997).

EMEA/CVMP/153b/97 – Note for Guidance on the Establishment of Maximum Residue Limits for Salmonidae and other Fin Fish (CVMP adopted 15 January 1998).

EMEA/CVMP/473/98 – Note for Guidance for the Determination of Withdrawal Periods for Milk (Adopted by CVMP 8 March 2000).

EMEA/CVMP/276/99 – Note for Guidance for the Assessment of the Effect of Antimicrobial Substances on Dairy Starter Cultures (Adopted by CVMP 8 March 2000).

EMEA/CVMP/187/00 – Note for Guidance on the Risk Analysis Approach for Residues of Veterinary Medicinal Products in food of animal origin (Adopted by CVMP 10 January 2001).

EMEA/CVMP/231/00 *Rev. 1* – Updated Application Software relating to Note for Guidance for the Determination of Withdrawal Periods for Milk.

EMEA/CVMP/234/01 – Revised Guideline on the Safety Evaluation of Antimicrobial Substances regarding the effects on Human Gut Flora (Adopted by CVMP 9 January 2002).

EMEA/CVMP/235/01 – Background Paper to the Revision of the CVMP Guideline on the Safety Evaluation of Antimicrobial Substances regarding the effects on Human Gut Flora (Released May 2001).

EMEA/CVMP/069/02 – Approach for Implementation of the Note for Guidance on the Risk Analysis Approach for Residues of Veterinary Medicinal Products in food of animal origin.

EMEA/CVMP/542/03 – Guideline on Injection Site Residues (CVMP adopted October 2004).

EMEA/CVMP/563/02 – Updated Application Software relating to Note for Guidance on Approach towards Harmonisation of Withdrawal Periods for Meat.

EMEA/CVMP/928/02 – Appointment and Responsibilities of Rapporteur and Co-rapporteurs for procedures regarding Veterinary Medicinal Products.

CVMP/VICH/525/00 VICH Topic GL22 Step 7 – Safety studies for veterinary drug residues in human food: Reproduction studies (*updated June 2004*).

CVMP/VICH/526/00 VICH Topic GL23 Step 7 – Safety studies for veterinary drug residues in human food: Genotoxicity studies (*updated June 2004*).

CVMP/VICH/645/01 VICH Topic GL28 Step 7 – Safety studies for veterinary drug residues in human food: Carcinogenicity testing (CVMP adopted November 2002).

CVMP/VICH/645/01-rev 1 VICH Topic GL28 Step 7 – Safety studies for veterinary drug residues in human food: Carcinogenicity testing (Released for consultation May 2004).

CVMP/VICH/484/02 VICH Topic GL31 Step 7 – Safety studies for veterinary drug residues in human food: Repeat Dose (90 days) Toxicity Testing (CVMP adopted November 02) (*updated June 2004*).

CVMP/VICH/485/02 VICH Topic GL32 Step 7 – Safety studies for veterinary drug residues in human food: Developmental Toxicity Testing (CVMP adopted November 02) (*updated June 2004*).

CVMP/VICH/486/02 VICH Topic GL33 Step 7 – Safety studies for veterinary drug residues in human food: General Approach to Testing (CVMP adopted November 02) (*updated June 2004*).

CVMP/VICH/467/03 VICH Topic GL36 Step 7 – Safety studies for veterinary drug residues in human food: General Approach to establish a microbiological ADI (CVMP adopted June 2004).

CVMP/VICH/468/03 VICH Topic GL37 Step 7 – Safety studies for veterinary drug residues in human food: Repeat-dose (Chronic) Toxicity Testing (CVMP adopted June 2004).

CVMP Position Papers relevant to the establishment of MRLs

EMEA/CVMP/274/96 – Position Paper on Requirements for LOQ/MRL Ratio (adopted January 1997)

EMEA/CVMP/029/97 – Position Paper on Selection of Target Tissues for the Establishment of MRLs under Council Regulation (EEC) No. 2377/90

EMEA/CVMP/072/97 Revised – Position Paper on the Definition of Substances capable of Pharmacological Action in the context of Council Directive 2001/82/EC as amended with particular reference to Excipients and Manufacturing Materials (CVMP adopted July 2004)

EMEA/CVMP/151/99-Final – Position Paper on Availability of Veterinary Medicines agreed on 17 March 1999.

EMEA/CVMP/731/99-Final *Updated* – Position Paper on Availability of Veterinary Medicines agreed on 14 October 1999.

EMEA/CVMP/411/00-Final *Updated* – Position Paper on Availability of Veterinary Medicines agreed on 21 June 2000

EMEA/CVMP/391/02 – Position Paper on the establishment of MRLs for Milk considering the daily intake by children (Released by the CVMP November 2002)

EMEA/CVMP/457/03 – Position Paper regarding Availability of Veterinary Medicinal Products – Extrapolation of MRLs (CVMP adopted December 2003).

EMEA/CVMP/477/03 – Position Paper regarding availability of Products for Minor Uses and Minor Species (MUMS) (CVMP adopted July 2004)