New provisions for the Regulation on Maximum Residue Limits

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List of Abbreviations

ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism and Excretion
ARD	Acute Reference Dose
ASDI	Acceptable Single Dose Intake
BMD	Benchmark Dose
bw	Body Weight
CRL	Community Reference Laboratory
CVMP	Committee for Veterinary Medicinal Products
EC	European Commission
EEA	European Economic Area
EEC	European Economic Community
FEAP	European fish producer association
EFSA	The European Food Safety Authority
EMEA	European Medicines Agency
EPMAR	European Public MRL Assessment Report
EPP-ED	European People's Party - European Democrats in the European Parliament
EU	European Union
FAO	Food and Agriculture Organisation
FDA	Food and Drug Administration
FEAP	Federation of European Aquaculture Producers
FEDESA	Fédération Européenne de la Santé Animale
GLP	Good Laboratory Practice
IFAH- Europe	International Federation for Animal Health Europe
ISO	International Organization for Standardization
JECFA	Joint Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
kg	Kilogram
LO(A)EL	Lowest Observed (Adverse) Effect Level
LOD	Limit of Detection
LOQ	Limit of Quantitation
mg	Milligram
MRL	Maximum Residue Limit
MSD	Minimum Significant Difference
MUMS	Minor Use and Minor Species
NO(A)EL	No Observed (Adverse) Effect Level
NOEC	No Observed Effect Concentration
NOEL	No Observed Effect Level
NRL	National Reference Laboratory
OECD	Organisation for Economic Co-operation and Development
OJ	Official Journal
PBPK	Physiologically Based Pharmacokinetic Modelling

QRD	Quality Review of Documents
RfD	Reference Dose
RPA	Reference Points for Action
SF	Safety Factor
SmPC	Summary of Product Characteristics
SPC	Supplementary Protection Certificate
SOP	Standard Operating Procedure
UF	Uncertainty Factor
US	United States of America
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
WHO	World Health Organisation
WIN	Work Instruction

1. Introduction

The main objective of the European Union (EU) legislation governing the licensing and marketing of veterinary medicines is to protect human and animal health. Veterinary medicinal products for food-producing animals can be authorised only if the foodstuffs produced will be harmless to consumers and do not contain residues of the medicine or its metabolites above the MRL.

Article 6 (1) of Directive 2001/82/EC, as amended [1], states:
“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”.
Regulation (EEC) No 2377/90 [2] as amended laying down a Community procedure to evaluate the safety of residues of pharmacologically active substances. The Annexes are regularly updated by Commission and Council Regulations which are published by the Commission on the DG Enterprise website [3].

According to this Regulation residues of veterinary medicinal products are defined as all pharmacologically active substances, whether active principles, excipients or degradation products, and their metabolites. Maximum residue limits (MRLs) have to be established for active substances and if applicable also for excipients (EudraLex - Volume 8) [4].

An MRL is defined as the maximum concentration of residues 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 recognized as acceptable in or on a food. The Committee for Veterinary Medicinal Products (CVMP) also publishes a list of substances [5] not falling within the scope of Council Regulation (EEC) No 2377/90 [2], as amended. These substances are classified as normal components of human food, biologically inert when orally taken, or non chemicals.The MRL Regulation does not apply to active substances of biological origin intended to produce or to diagnose active or passive immunity used in immunological veterinary medicinal products.

The time between the last medication of a food producing animal and the time when the level of residues in the tissues or products (muscle, liver, kidney, milk, eggs, honey or other edible products) is lower, or equal to the MRL determines the withdrawal period/withholding period. Until this time has elapsed, the animal or its products must not, by law, be used for human consumption. Withdrawal periods exist so that MRLs are not exceeded and to ensure consumer safety. As a result, although residues above the MRL should not occur, even if they do, they generally present no risk to the consumer because of the very large safety margins used in setting the MRL.

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 a safety assessment.

The current regulation contributed to protect human and animal health and welfare but it also had a strong impact on the availability of veterinary medicinal products, especially for food producing animals. To overcome this problem, the European Commission suggested to review the existing regulation.
The aim of this thesis is to describe the current regulation and the problems associated with it, as well as the new proposal [6], which will replace the current regulation. It is discussed, to which extend the new proposal provides changes to overcome the existing problems and which further approaches could help to improve the current situation.

2. Regulation (EEC) No 2377/90 – the MRL Regulation

2.1. Principles of the “old MRL Regulation”

On 26 June 1990 the Council adopted Regulation (EEC) No 2377/90 [2] laying down “a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin”. Consequently, pharmacologically active substances could not be used without positive evaluation in food producing animals. After a transition period from 1 January 2000 onwards veterinary medicinal products without a MRL have been withdrawn from the EU market.

The primary goal of this regulation is to ensure food safety and hence the protection of human health. Another important aspect is to allow the free movement of food of animal origin within the entire EC - market.

The central aspect of Regulation (EEC) No 2377/90 [2], as amended is the establishment of maximum residue limits (MRLs) for veterinary medicinal products in foodstuffs of animal origin if considered necessary.

Regulation (EEC) No 2377/90 [2], as amended is assessing the safety of residues by combining risk assessment, risk management and risk communication [7].

- **Risk assessment** is a first step in a risk management process, starting with the identification of a hazard which may cause adverse effects towards animal health followed by the determination of the probability of occurrence. This hazard then has to be characterised, analysing it qualitatively and/or quantitatively. At this stage the acceptable daily intake (ADI) is established. Using a marker residue an estimation of the consumer intake can be performed to get a view on the exposure assessment. The last step in the risk assessment is the risk characterisation where it is decided, whether an MRL needs to be established. Therefore the risk has to be estimated qualitatively and/or quantitatively to which the consumer may be exposed to residues resulting adverse effects to human health.
- **Risk management** is a tool consisting of several steps to reduce or avoid a risk by using strategies to control the risk (e.g. the establishment of withdrawal periods following the assessment of new pharmacologically active substance in the MRL procedure, which normally leads to the inclusion into Annex I – IV of Council Regulation (EEC) No 2377/90 [2], as amended).
- **Risk communication** is the process in which all information relating the risk are communicated to all parties involved and interested in the process (e.g. EMEA Summary Reports).

2.2. Establishment of MRLs

The main principle for the MRL assessment is summarized in the Guideline "Note for guidance on the risk analysis approach for residues of veterinary medicinal products in food of animal origin" [7]. Information and particulars to be included in an application for the establishment of a maximum residue limit for a pharmacologically active substance used in veterinary medicinal products are listed in ANNEX V of Council Regulation (EEC) No 2377/90 [2], as amended, in the EudraLex - Volume 8 [4]. and on the homepage of the

European Medicines Agency (EMEA) [8]. Also the EMEA Standard Operating Procedures (SOP) and Work Instructions (WIN) should be followed. The application shall also conform with the principles laid down in Directive 81/852/EEC [9] and the articles 52 and 53 of Regulation (EEC) No 2309/93 [10].

Studies should be performed according to the Guidelines of the CVMP and Good Laboratory Practice (GLP) [11]. Also the CVMP Note for Guidance on the Establishment of Maximum Residue Limits for Minor Animal Species [12] should be taken into consideration.

About 3-4 months before the submission of an application for the establishment of MRLs, the applicant has to contact the EMEA. After the CVMP meeting at which the letter of intent is considered, the applicant will be notified about the procedural details.

The time line for an MRL application is defined in article 6 of Council Regulation (EEC) No 2377/90 [2], as amended. The MRL application should be submitted at least six months before the submission of the dossier (Article 12 of Directive 2001/82/EC, as amended). The CVMP has to give its opinion within 120 days after receiving the application (120-day time limit without clock-stop for questions; the time frame for answers is normally 6 months).

To apply for an MRL the applicant has to supply a dossier consisting of a safety and a residues documentation to the CVMP which prepares the assessment.

All data which have to be provided and studies/testings which have to be performed are described in the documents mentioned above. Therefore only the most important points are summarized in the following.

2.2.1. Safety documentation

The Safety Documentation (Part III A of the dossier) contains all the pharmacology and toxicology studies carried out with the medicine in laboratory animals. These studies examine what happens to the substance in the body and assess how much can be given safely, without inducing any unwanted adverse effects.

From a series of required toxicological studies a No Observed Effect Level (NOEL) is established (expressed in mg/kg), below which administration of a certain dose of a product has absolutely no effect on the animal, either clinically, toxicologically or biochemically. In certain cases the NOEL is also expressed as no observed (adverse) effect level (NO(A)EL) or, the lowest observed (adverse) effect level (LO(A)EL).

The NOEL is divided by a safety factor to give extra safety for human consumers. It is therefore prudent to adjust for possible differences by assuming that humans are more sensitive than the most sensitive test animal.
Traditionally a safety factor of 100 has been used, to account for the differences between test animals and humans (factor of 10) and possible differences in sensitivity between humans (another factor of 10). The World Health Organisation (WHO) recommends a safety factor of between 100 and 1000 (usually depending on the type of effect).

The NOEL is used to determine the Acceptable Daily Intake (ADI) of the product which may be consumed by a human being without causing any adverse effect.

More specifically, the ADI is defined as the amount of a specific substance in food or drinking water that can be ingested per day over a lifetime without a measurable pharmacological, toxicological or microbiological effect (expressed in mg/kg body weight/day or, referring to a average human bodyweight of 60 kg).

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

This concept was first introduced in 1957 by the Council of Europe and also later by the Joint Expert Committee on Food Additives (JECFA). The ADI may be set on the basis of toxicological, pharmacological or microbiological data, whichever is the lowest [7].

The estimation of the consumer intake also takes into account the residue concentration in the food commodities derived from the pattern of residue depletion of the substance in the target animal. Where appropriate residues from the pesticide use of a substance are also taken into account.

For antimicrobial substances there is an additional safety assessment to determine a microbiological ADI, based on the effect of the substance on the normal gut bacterial flora found in humans (methodologies for establishing a microbiological ADI are described in the VICH guideline 36 (CVMP/VICH/467/03-FINAL-corr) [13]). For the calculation of microbiological ADIs based on *in vitro* data, safety factors are already included in the formula. For *in vivo* models the safety factors is calculated in the same way as for the toxicological ADI. The substantial safety margin used to calculate the ADI is considered necessary to cover the substantial uncertainties in the models used and their relevance to a diverse population of consumers.

According to EudraLex - Volume 8 [4], “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”.

In the safety documentation, also official assessments of CVMP, JECFA and JMPR (Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues), should be included. The safety documentation is completed by an expert report.

2.2.2. Residue documentation

The Residues Documentation (Part III B of the dossier) contains all the data concerning the formation, nature, behaviour and disappearance of residues after a medicine has been given to a food producing animal which are necessary to determine the withdrawal period. The additional data necessary to determine MRLs are based on the results contained in the safety documentation.

Residues of veterinary medicinal products (in accordance with Article 1 (1) (a) of Council Regulation (EEC) No 2377/90 [2], as amended), are defined as 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 has been administered.

A tool to assess the MRL are marker residues which are identified on the basis of pharmacokinetic and depletion studies. Marker residues are substances or metabolites which decrease in a known relationship to the concentration of total residues in tissues, eggs, milk or other animal tissues. The marker residue is not necessarily a residue of toxicological or microbiological concern and has to be mentioned in the residue documentation. When

establishing a MRL, consideration is also given to residues that occur in food of plant origin and/or come from the environment.

The residue levels that can remain in tissues are called the MRLs. Where necessary, MRLs should be established for all food commodities (muscle, fat (fat and skin where appropriate), liver and kidney, meat of fin fish (muscle and skin in natural proportions), milk, eggs and honey) from food producing animals.

The maximum concentration of residue following administration of a veterinary medicine are determined in such a way that the sum of the residues (which may cause a health risk) in a defined daily consumption portion (Standard Food Basket) of the food of animal origin does not exceed the ADI. The calculation assumes an average daily food intake of 500 g meat and offal[*] or 300 g fish, 1,5 l milk, 100 g eggs and 20 g honey.

For the documentation also data from literature and if possible data which refer to similar substances should be provided.
The applicant and the expert (writing the expert report for the Residue documentation) 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 Council Regulation (EEC) No 2377/90 [2], as amended.

Applicants have to submit also the validated analytical method for all the tissues for which MRLs have been set (as required in Annex V to Council Regulation (EEC) No 2377/90 [2], as amended). This method should be validated across a range which at least includes one-half and twice the MRL and it also should determine the marker residue on which the MRLs are based. Commission Decision 2002/657/EC, as amended [14] establishes criteria and procedures for the validation of analytical methods to ensure the quality and comparability of analytical results generated by official laboratories.

2.2.3. MRL Assessment

MRLs are set by the European Commission (EC) or the Codex Alimentarius Commission.

The Codex Alimentarius (Codex) was established in 1963 by FAO (Food and Agriculture Organisation) and WHO (World Health Organisation). The Codex aims to protect the health of consumers, ensure fair trade practices in the food trade, and promote co-ordination of all food standards work undertaken by international governmental and non-governmental organisations [15]. It aims to enable the harmonisation of food standards and is used by the WTO (World Trade Organization) as the benchmark against which national food safety is measured. The Codex MRLs are set as standards for food and they are not statutory for the authorization of pharmacologically active substances in veterinary medicinal products in the EU. Since September 2008 all statutory MRLs regarding foods treated with pesticides are listed in EC Regulation 396/2005(EC) [16].

Therefore, the assessment for an MRL regarding active substances in veterinary medicinal products in the EU is set on a case-by-case basis by the EC after adoption by the Standing Committee, following an opinion of the CVMP.

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

The assessment of a new pharmacologically active substance in the MRL procedure normally leads to the inclusion into Annex I – IV of Council Regulation (EEC) No 2377/90 [2], as amended:

Annex I: List of pharmacologically active substances for which maximum residue levels have been fixed (Substances with final MRLs)
The data in the dossier are considered adequate to establish a final MRL.

Annex II: List of substances not subject to maximum residue levels (Substances for which MRLs are not necessary)
The data in the dossier demonstrate that there is no risk to the consumer and MRLs are not needed. The application of some substances is subject to restrictions (e.g. only external use or restricted for described animal species).

Annex III: List of pharmacologically active substances used in veterinary medicinal products for which maximum residue levels have been fixed (Substances with provisional MRLs)
This is for medicines for which MRLs can be established but some clarification of further studies are required before final MRLs can be set. The provisional MRLs are valid for a maximum of 5 years.

Annex IV: Lists of pharmacologically active substances for which no maximum levels can be fixed (Substances that cannot have an MRL)
Residues of the medicine pose an unacceptable risk to the consumer or there is insufficient information to allow a full assessment. The products in Annex IV are prohibited for use in food producing animals in the European Union.

If a substance can not be included in Annex I-IV (e.g. insufficient data were presented for evaluation to the CVMD) this also means that the substance may not be used for treatment of food producing animals.

The applicant has the right to appeal against the CVMD opinion within 15 days after receipt (in accordance with Article 7 of Council Regulation (EEC) No 2377/90 [2], as amended). Otherwise, 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 Council Regulation (EEC) No 2377/90 [2], as amended.
The annexes are regularly updated by Commission Regulations which are then published in the Official Journal (OJ) of the European Communities and on the European Commission website [17]. Additionally, the European Public MRL Assessment Report (EPMAR, formerly called Summary Report) is published containing more detailed information.

Since 1 January 1992 the MRL has to be published before a veterinary medicinal product for food producing animals can be registered in the EU. Older pharmacological active substances had to be assessed until 1 January 2000. Due to article 14 of Council Regulation (EEC) No 2377/90 [2], as amended, since 1 January 2000 the administration of veterinary medicinal products containing pharmacological active substances for which no MRL was accomplished to food producing animals is forbidden in the EU.

The CVMP issued in 1995 a list of substances [18] not falling within the scope of Council Regulation (EEC) No 2377/90 [2], as amended, because some substances were normal components of human food, biologically inert when orally taken, or not classified as

chemicals. This list is regularly updated and includes also substances for which no formal MRL application had been made and substances which were originally the subject of an intention to submit or even an actual application but subsequently classed as not within the scope of Council Regulation (EEC) No 2377/90 [2], as amended.

Once the MRL is published, it has to be inserted into the dossier Part IIIB (according to Volume 6B - Notice to applicants - Presentation and content of the dossier).

The MRL is not protected and can be referred to by any pharmaceutical company for the application of a marketing authorisation of a veterinary medicinal product.

2.2.4. Establishment of a withdrawal period

The determination of withdrawal periods is a complex affair, but considered essential to ensure the safety of the consumer.

Once MRLs have been published (EMEA Summary Reports) sequentially in the Official Journal of the EU (arbitrative) and on the EMEA homepage [17], it is then necessary in the context of granting a marketing authorisation (in accordance with Directive 2001/82/EC as amended and Regulation 726/2004/EC) to determine a withdrawal period for veterinary medicines; this ensures that residues from the product concerned will not exceed the MRLs.

The time between the last medication of a food producing animal and the time when the level of residues in the tissues or products is lower, or equal to the MRL determines the withdrawal period required before animals can be sent for slaughter and used for human consumption.

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. The withdrawal period depends on the active substance, composition of the excipients, pharmaceutical form, route and duration of application. It is product specific and species specific.

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.”

Therefore a dossier has to be submitted to the responsible authorities consisting of part I - IV (in accordance with Volume 6 - Notice to Applicants: Veterinary Medicinal Products). The two parts of the dossier on safety and residues which have been used for the MRL assessment (in accordance with Council Regulation (EEC) No 2377/90 as amended and Notice to applicants Vol. 8) have to be completely included as Part III A (Safety) and Part III B (Residues), (except points (i), (ii) or (iii) of Article 13(1)(a) of Directive 2001/82/EC have been submitted).

The applicant and the expert (writing the expert report for the Residue documentation) propose withdrawal periods for all food producing animal species taking into account the proposed MRL based on the following guidelines which are available on the EMEA website [19]:

Notes for Guidance regarding withdrawal periods for animal tissues (EMEA/CVMP/036/95) [20] and milk (EMEA/CVMP/473/98) [21] were published by the CVMP in order to ensure a uniform approach to establish withdrawal periods throughout the EU (EEC). Corresponding computer programs for the calculation of the withdrawal periods in accordance with these guidelines are available on the EMEA website in the same section.

The withdrawal period is assessed during the registration process of the veterinary medicinal product. Depending on the procedure chosen by the applicant to obtain a marketing authorisation for the veterinary medicinal product, proposed withdrawal periods will either be approved by a Member State (national, decentralized or mutual recognition procedure), or by the CVMP (central procedure).

Once the withdrawal period is assessed, the SmPC, primary and secondary packaging materials, package leaflet (according to the QRD templates) [22] and also the dossier (Part IIIB and expert report) have to be updated, if necessary. A change in the composition of the product may cause a different withdrawal period.

For equidae there is a special situation. A list of substances essential for the treatment of equidae is published in the Council Regulation No 1950/2006 [23]. Veterinary medicinal products without a MRL for equidae, or used "off-label", or used under the “Cascade” provision and which are not on "the essential" or the "positive list" for equidae referred to in Article 10(3) and 11 of Directive 2001/82/EC and which are not administered intra-muscularly or subcutaneously are subject to a withdrawal period of at least six months.

2.3. Problems and consequences of the current MRL Regulation

The Community legislation on residues of pharmacologically active substances (Council Regulation (EEC) No 2377/90 [2], as amended) is a complex system which is distributed over several pieces of procedures and legislative tools. On one hand the implementation of the legislation has increased the consumer protection, animal health and animal welfare but on the other hand the current inflexibility is resulting in numerous difficulties:

- **Reduced number of medicines available for food-producing animals**

  The requirement of establishing MRLs is associated with high costs for collecting the required scientific data and assembling the documentation. These data include information and studies on the pharmacology, toxicology, pharmacokinetics and depletion of residues of the pharmacologically active substances (and their metabolites) from the target tissues for all animal species applied. Also the validated methods for the detection and quantification of the residues have to be provided.
  These additional costs result in a reduced number of veterinary medicinal products available in Europe for the treatment of food-producing animals to an extent that creates adverse problems in the medical care for public and animal health and welfare.

  Already in 1995 the Federation of European Aquaculture Producers (FEAP), produced a list of 62 therapeutic agents (excluding vaccines) which were used in fish farming in the EU (FEAP 1995): of those 43 were absolutely needed and only 27 were likely to be authorised to remain on the market after the completion of the MRL evaluation, i.e. by the end of 1999 [24].

  Council Regulation (EC) 1950/2006 [23] provides a list of substances essential for the treatment of equidae, which are also affected by the decreased number of medicinal products available for food producing animals. The withdrawal period for each of the listed substances for equidae intended for slaughter for human consumption shall be at least six months.

- **Strict limitations on the flexibility allowed to veterinary surgeons in using or prescribing veterinary medicines**

  Another effect of the reduced number of veterinary medicinal products available is that veterinary surgeons increasingly have to adopt the “Cascade” provision, which means that the product is being used under their personal responsibility. Against the background of this provision veterinary surgeons are in exceptional cases allowed to prescribe medicines ‘off-label’ within very strict limitations if it is necessary to avoid unacceptable suffering and where no suitable product exists for the treatment of an animal under his/her direct personal responsibility. The veterinary surgeon also has to set an appropriate withdrawal period for the slaughter of treated animals or for the production of milk, eggs or honey. But even using the “Cascade” provision according to Article 10 and 11 of Directive 2001/82/EC [1], some therapeutic gaps remain.

- **Problems related to the control of residues in foods of animal origin**

  In the EU, the veterinary pharmaceutical companies are responsible for the production of veterinary medicinal products in accordance with the corresponding marketing authorisations. The Member States are responsible for the control of residues resulting from the use of these products.

  In 2004 the Regulation (EC) No 882/2004 [25], as amended was introduced to ensure the verification of compliance with feed and food law, animal health and animal welfare rules. This regulation has improved the residue control in the Community and contributed significantly to the harmonisation of control, but it also was criticised e.g. because of its inflexibility (it was impossible to react to recent residue findings and delay in obtaining and evaluating of results and sampling requirements).
  With the current legislation, international standards supported by the EU cannot be included in Community legislation without a new scientific assessment by the EMEA.

- **Classification of all pharmacologically active substances into a specific annex**

  Article 6 of Directive 2001/82/EC [1] requires the inclusion of a pharmacologically active substance in annexes I, II or III of Regulation 2377/90 as a precondition for obtaining a marketing authorisation for veterinary medicinal products for food producing animals.

- **Limitations in the extrapolation of MRLs from one species to another**

  After implementation of Council Regulation (EEC) No. 2377/90, the CVMP already realized, that there was a need for a more pragmatic approach for the extrapolation of MRLs from one species to another, especially those classified as minor species. Therefore several CVMP proposals were published (e.g. EMEA/CVMP/153a/97 [12], EMEA/CVMP/153b/97 [26], EMEA/CVMP/187/00-FINAL [7], EMEA/CVMP/069/02 [27]), resulting only in a slight improvement regarding the availability of veterinary medicinal products.

- **Insufficient procedures for the establishment of a short-term risk assessment for certain residues detected in imported food**

  Residues of substances not authorised in the EU should not be present in imports to the EU. In food imported from third countries, residues from substances not authorised in the EU have been detected from different Member States at differing concentrations. The Member States which didn’t detect the residues or found them to be below the MRL accepted this food for import, the others rejected it, which leads to a dis-harmonisation within the EU. The Member States also do not have reference points of action (RPA) in particular for substances detected in food from third countries.

- **The current legislation is difficult to understand**

  The current legislation is a complex system which is partly circuitous and mistakable formulated.

Additional reasons for criticism are the complexity, data requirements for the MRL documentation and the additional scientific assessment for Codex MRLs causing high costs and problems in comprehensibility.

2.4. MRL Reflection Paper on Residues in foodstuffs of animal origin

In December 2003 a Reflection Paper [28] was published by the Commission analysing the difficulties (mainly decreased availability of medicines and problems related to international trade) of the current Community legislation concerning residues of pharmacologically active substances in veterinary medicinal products for food producing animals.

The main issues of the Reflection Paper on which comments and proposals are solicited are the following:

- Structures for the appropriate differentiation of risk assessment and risk management for the evaluation and control of residues in food of animal origin
- Procedures for extrapolation of maximum residue limits
- Procedures for provision of reference points for control purposes
- Procedures for precautionary measures for substances in imported foodstuffs
- Procedures for short-term risk assessments in crisis situations
- Procedures for the evaluation of Third Countries residue control measures
- Procedures for the nomination of Community reference laboratories
- Procedures for the establishment of plans for monitoring and targeted controls
- Financing of measures of interest to the Community related to food safety
- Residue control specific enforcement measures

2.4.1. Comments on the Reflection Paper

Comments on the Reflection Paper from more than 40 sources (e.g. EMEA, Member States, countries outside the EU, animal health industry, organisations of the European food industry, individual persons) were received and analyzed [29, 30].

The majority of comments were related to the following 7 topics:

1. General comments

- More flexibility and harmonization (e.g. for risk analysis and residues control)
- Avoidance of new studies resulting in higher costs and less available medicines
- Reorganisation of the annexes to Regulation (EEC) No 2377/90 as amended

- Clear scopes and definitions

2. Residue monitoring and enforcement

- Harmonised sampling procedures, reporting and action in relation to non-compliance
- Reorganization of national monitoring plans to save resources
- Sample selection according to risk analysis principles and occurrence of prohibited substances
- Establishment of a feedback mechanism between the residue evaluation procedure according to Regulation (EEC) No 2377/90, as amended, and the monitoring
- Spread of the monitoring activities (Exposure, Community targeted, national/ad hoc targeted on suspicion)
- Review of substances in Annex I of Directive 96/23/EC and deletion of contaminants
- More self-regulatory approaches concerning the product responsibility

3. Imports of food from third countries

- Regularly up-dated evaluation of third countries according to authorisation schemes, control of production and use, identification of prohibited substances and monitoring plans
- Harmonised sampling plans and sampling procedures following risk assessment principles as within the Community (same methods and detection limits)

4. Minimum requirement performance limits and zero tolerance

- Review and modification of the legislation on prohibited substances (e.g. zero tolerance approach for prohibited substances as in Annex IV of Regulation (EEC) No 2377/90 as amended, but also regarding all substances prohibited under Directive 96/22/EC [31])
- Establishment of harmonised ‘action limits’ for the evaluation of food that contained residues of these substances (based on laboratory performance capabilities and a basic toxicological evaluation)
- Setting of default limits (temporary in case of urgent need)
- Harmonised reporting and enforcement measures in case of unauthorised use

5. Structure and performance of the Community reference and control laboratories

- Review of the CRL (Community Reference Laboratory) and NRL (National Reference Laboratory) network (e.g. workload, competence, development and validation of methods, adequate financing to ensure independence)

6. Risk analysis

- Review and differentiation/separation of risk assessment and risk management (not entirely possible in all cases)
- Risk assessment should also focus more on estimates of real consumer exposure to residues (in case of missing data, default levels should be introduced)

- Proposals for risk management options, including other legitimate factors, could form part of the risk assessment
- Harmonised risk analysis procedures for all types of residues (for veterinary medicines, pesticides and feed additives as well as contaminants)
- Risk/benefit analysis of substances used in veterinary medicinal products
- Review and Re-evaluation of existing MRLs
- Adoption of agreed Codex Alimentarius MRLs as EU standards
- Temporary risk assessments (e.g. in crisis situations)
- Find responsible body for risk evaluation of (and set limits for) residues of non-authorised substances (e.g. EMEA or EFSA)

7. Availability of veterinary medicinal products in the EU

- The implementation of Council Regulation (EEC) No 2377/90, as amended on MRLs has contributed to reduce the number of medicines available for food-producing animals (lack of authorised veterinary medicinal products for fresh-water fish and bees)
- Review of data requirements for the establishment of MRLs (e.g. validation of the residue analytical method)
- Introduction for extrapolation of MRLs to additional species (based on scientific principles)
- Data protection for MRL documentations

2.4.2. Consultation of interested parties and impact assessment

After publication of the Reflection Paper the Member States organized meetings in 2004 and 2005 where ideas for legislative amendments were discussed. These proposals had been identified by six expert Working Groups. The European Commission also requested the stakeholders to complete a specific questionnaire which was then evaluated by the Expert Working Groups. The results were summarized in an impact assessment [32] with three main policy options:

- **Option 1 - Maintain the current legal framework.**

  Nothing would change so the problems would be unresolved (e.g. availability of veterinary medicinal products for food producing animals).

- **Option 2 - Review the existing regulation.**

  The shortcomings of Regulation (EEC) No 2377/90 [2], as amended, will be corrected by incorporating specific legal provisions and amending existing rules, while leaving the overall system of setting MRLs based on scientific assessment intact.

- **Option 3 - Replace the existing legislation by guidelines.**

  This would on the one hand simplify the legislative requirements resulting in more flexibility for both competent authorities and to the industry, on the other hand it would result in a deregulation (e.g. different levels of food safety). It was concluded that this option does not meet the objectives and purposes defined by the Commission.

2.4.3. Conclusions and next steps

Based on the comments the Commission will analyse the different topics and propose amendments to the current legislation. This should improve consumer protection, animal health, welfare and trade requirements concerning residues of pharmacologically active substance used in veterinary medicinal products in food producing animals. Also it is aimed to harmonize the new legislation with the Food Law [33] and approaches regarding residues from use of feed additives, pesticides and biocides, where appropriate.
This would in conclusion result in a more consistent approach for the risk analysis and control of residues of such substances, which may appear in food produced in or imported into the European Union.

3. EC proposal for a Regulation to replace Regulation 2377/90

The current Regulation (EEC) No 2377/90 [2], as amended, guarantees a high level of public health protection but it contributed to several problems. On 17 April 2007 the European Commission adopted the “Proposal for a Regulation of the European Parliament and of the Council laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, and repealing Regulation (EEC) No 2377/90” [6] based on Article 152 (4) (b) of the EC Treaty (triggering the start of the co-decision procedure with the European Parliament and the Council of the EU).
The proposal is reflecting the consultation on possible changes launched in 2004 by the Commission. The current regulation will be modified, but the principle of the MRL assessment will be retained.

The new proposal of the Commission has four main objectives:

1. To improve the availability of veterinary medicinal products for food producing animals in order to ensure animal health and welfare and avoid illegal use of substances

2. To simplify the existing legislation by enhancing readability of the provisions on established MRLs for the end-users (i.e. animal health professionals, control competent authorities in Member States and third countries)

3. To provide clear references for the control of residues of pharmacologically active substances in foodstuffs to improve consumer health protection and the functioning of the 'single market'

4. To clarify the Community procedures establishing MRLs by ensuring consistency with international standards

The proposal for the new Regulation aims to review and simplify existing provisions related to the establishment of MRLs for residues of pharmacologically active substances in veterinary medicinal products legally accepted in foodstuffs of animal origin. There will be a separation for the procedure to set MRLs from the procedure to apply for a marketing authorization.
Additionally it aims to continue to limit consumer exposure to residues of pharmacologically active substances in foodstuffs of animal origin thus to improve the level of animal welfare, animal health and consequently ensure a high level of consumer health protection. The

regulation should improve the availability of veterinary medicinal products in the Community and reduce the off-label use.

These objectives can be reached by introducing the following changes to the current Regulation:

- **Extrapolation of MRLs to other species**

  Because of the high costs of increasing regulatory requirements for the establishment of MRLs for use in food-producing species has led to a reduced number of authorised medicines available for minor species (e.g. goats and bees) or therapeutic classes in the EU.
  The new Regulation proposes to establish principles to extrapolate data on metabolism and residue distribution of pharmacologically active substances (MRLs) which have been set for a specific species to other species and/or foodstuffs, where an authorised product is not available. A risk assessment can be performed by independent experts. So no new data have to be provided and additional costs are avoided. The principles for extrapolation will be a compulsory part of the overall scientific assessment.

- **Adapt Codex MRLs without a further risk assessment**

  MRLs are set by the European Commission or the Codex Alimentarius Commission. The EU is a member of the Codex and thus involved in the MRL assessment of the Codex Alimentarius Commission. Currently for Codex MRLs a further risk assessment is conducted before they are accepted by the EU.
  The new Community legislation introduces an obligation to adapt Codex MRLs without further risk assessment, assumed that the scientific basis is adequate to avoid any risks for animal and human health. So no separate scientific assessment of active substances which have been assessed by the Codex Alimentarius Commission have to be performed. This results in reduced costs, an accelerated time period to obtain a marketing authorization and thus in more medicinal products available for food producing animals.

- **Create a legal framework to set MRLs for substances not authorized in the EU**

  Based on Council Regulation (EEC) No 2377/90 [2], as amended, veterinary medicinal products for food-producing animals without a MRL have been withdrawn from the EU market. The problem is imported food containing substances not authorised for use in the EU. Some of these substances are banned, but others were never assessed. Until now for these residues the principle of ‘zero tolerance’ was applied which was complicated by the increasing analytical possibilities to detect residues at ever lower levels.

  Some EU countries started to set their own limits resulting in a disharmonisation within the Community. In 2002 and 2005 the Commission adopted Commission Decision 2002/657/EC and Commission Directive 2005/34/EC [14, 34], which established minimum required performance levels (MRPLs) for banned substances found in exports from third countries, based on the analytical levels which the control laboratories in all Member States would be able to detect.
  The new proposal is intended to help to create a legal framework to establish MRLs for pharmacologically active substances not intended for use in veterinary medicinal products in the EU. In the case MRLs have not been set, RPAs should be established and communicated to the European Food Safety Authority (EFSA). For the suitability of these RPAs a risk assessment will be performed by EFSA. This will improve the international trade of foodstuffs and mainly ensure a high level of consumer health protection.

- **MRL assessment for substances used as biocides in animal husbandry**

  The legal framework is presented in the Biocides Directive [35]. Residues of Biocides (such as disinfectants) used for animal treatment may also occur in foodstuffs.
  Therefore, the Commission suggested to set MRLs for pharmacologically active substances used in Biocides. The assessment procedure should be comparable to the assessment procedure for the establishment of MRLs for pharmacologically active substances used in veterinary medicinal products. Also the unsolved problem of the fees for the assessment will be addressed in the new legislation, because until now biocides fall under the European Food Standards Agency's responsibilities.

- **Simplification and better regulation of the legislation**

  The current legislation is a complex system which is distributed over several pieces of procedures and legislative tools. The review of the MRL Regulation proposes to reorganize the complete legislation and to integrate the MRLs (currently arranged in 4 annexes) in a single Regulation and perhaps to arrange them in an alphabetic order. The readability and comprehensibility of the regulation should be improved. This will also enhance the compliance, especially for third countries exporting foodstuffs of animal origin in the Community.

- **Other topics**

  To ensure human and animal health and welfare, the Commission may grant urgent authorizations. If required, the Parliament has to establish provisional MRLs (based on Council Regulation (EEC) No 2377/90 [2], as amended) for a period not exceeding five years.

  It is proposed to achieve more flexibility regarding the availability of veterinary medicinal products for horses. If the medicine does not have a MRL for equidae, which are not included in Annex IV or in Article 13(2) of Regulation (EEC) No 2377/90 [2], as amended, or which are:

  - used "off-label", as defined in Article 1(16) of Directive 2001/82/EC
  - used under the cascade provision
  - not administered intra-muscularly or subcutaneously
  - not on "the essential" or the "positive list" for equidae referred to in Article 10(3) of Directive 2001/82/EC

  shall have a nominal withdrawal period of six months to ensure that consumers are not exposed to unacceptable residues.

Some member states stressed the need to request an opinion from the Agency (EMEA) under certain conditions on MRLs for substances not intended to be used in veterinary medicinal products to be placed on the market in the Community (such as biocidal products).

Another problem are substances, which are used for different purposes (such as pesticides and veterinary medicinal products) because they may have different MRLs, published in different pieces of the legislation.

Also discussed amendments were a regularly review for RPAs because of the developing analytical methodology which could lead to an endless chase towards zero residues, or the amendment for an additional safety factor when extrapolating MRLs between species.

The draft which the Commission submitted on 17 April 2007 will supersede the current legislation, Council Regulation (EEC) No 2377/90 [2], as amended, which “lays down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin” after adoption by the co-decision procedure between the European Parliament and the Council. On 26 September 2007, the European Economic and Social Committee delivered its opinion and on 17 June 2008 the first reading took place at the European Parliament. More than 100 amendments were proposed. Finally, the European Parliament adopted the common position by 660 votes to 13 with 5 abstentions which was adopted on 18 December 2008 by the Council.

The common position of the Council on the adoption of a proposal for repealing Regulation (EEC) No 2377/90 of 08 January 2009 [36] addresses the availability of veterinary medicinal products, the adoption of Codex Alimentarius MRLs without further scientific assessment and reference points for action as key amendments and modification proposals.

In the Draft Recommendation for second reading of 23 January 2009 [37], the following key issues were discussed:

- Reference points for action to protect human health and the food chain
- Inclusion of relevant scientific findings of the European Food Safety Authority
- Scientific risk assessment to protect human health
- Inclusion of toxicological, pharmacological or microbiological effects in humans
- Withdrawal period of six months for equidae
- Urgent authorisations with a provisional MRL for a maximum of five years
- Opinions on MRLs for substances not intended for use in veterinary medicinal products to be placed on the market in the Community
- Methodology of the risk assessment and risk management
- Accelerated procedure for MRL assessment for urgent authorisations (opinion within 150 days)
- Prohibition for foodstuffs of animal origin containing pharmacologically active substances without an MRL
- Import prohibition for substances banned within the EU
- Experience report of the Commission on the new regulation after 5 years

In the Draft Recommendation for second reading on the Council common position for adopting a regulation of the European Parliament and of the Council laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, repealing Council Regulation (EEC) No 2377/90 and amending Directive 2001/82/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council (15079/2/2008 – C6-0005/2009 – 2007/0064(COD)) [37], a new clause for equidae was included.
Veterinary medicinal products without a MRL for equidae, or used "off-label", or used under the “Cascade” provision and which are not on "the essential" or the "positive list" for equidae referred to in Article 10(3) of Directive 2001/82/EC and which are not administered intra-muscularly or subcutaneously, shall have a nominal withdrawal period of six months (as already stated in Council Regulation No 1950/2006 [23]) to ensure that consumers are not exposed to unacceptable residues.

The European Parliament has appointed Avril Doyle (European People's Party - European Democrats in the European Parliament (EPP-ED), Ireland) as rapporteur, who recommends the adoption of the Common Position by the Environment Committee and the Plenary without modification or amendment as it reflects in its entirety the agreement reached with Council and the Commission.

These new provision is expected to stimulate innovation and the adoption will lead to an repeal of the existing legislation.

As legislative proposal a Regulation is proposed because it is directly binding. In comparison a Directive would have to be implemented into national law. The proposed act concerns an EEA matter and should therefore extend to the European Economic Area.
Furthermore, the Commission has agreed to make a declaration on an assessment of options for a future revision of Directive 2001/82/EC.

3.1 How to extrapolate MRLs

3.1.1. Previous guidance

The Pharmacokinetic properties absorption, distribution, metabolism and excretion (ADME) and the resulting toxicokinetic considerations can differ from species to species. In practice, MRLs for a particular substance are similar, so data can be extrapolated from major to minor species if they are physiologically similar.
Also in the Notice to applicants and Guideline Volume 8 [4] it is mentioned, that “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.”
If a wide safety margin was obtained in a major species, no tolerance studies for physiologically similar minor species are required. Also if three major target species (including monogastric and ruminant mammals and poultry) showed a comparable and wide margin of safety (at least ten), no additional tolerance studies are required for non-physiologically similar minor species (e.g., horses, rabbits) [38].

For horses there is the special situation, that in the EU, they are a food-producing species and a minor species. This led to discussions concerning the application of Council Regulation (EEC) No 2377/90 [2], as amended to active substances of products used in horses.

The current Regulation (EEC) No 2377/90 [2], as amended, contributed to a decrease in availability of medicines for food producing animals in the Community. The CVMP analysed this problem and suggested to establishing a more pragmatic approach, especially for minor species without compromising consumer safety. Therefore several CVMP proposals were published.

Already in the CVMP Note for Guidance on the Establishment of Maximum Residue Limits for Minor Animal Species, EMEA/CVMP/153a/97 [12], issued in 1997 and 1998 an approach for the extrapolation of existing MRLs from major species to minor species was foreseen. According to this guidance, “a substance is included in Annex I, II or III to Council Regulation (EEC) No. 2377/90 for a major animal species extrapolations to the corresponding minor

animal species can be made". This principle is applied within species families/classes (e.g. ruminants) without compromising consumer safety.
Extrapolations from major animal species to the corresponding minor animal species can be made for example from meat of cattle and sheep to other ruminant meat or from *Salmonidae* to other fin fish.

For major species a complete set of data including validated methods for the MRL assessment should be provided, based on specific residue data. Assuming that the exposure assessment for the different species would be similar, for minor species only a reduced data package in respect to residue data and analytical methods is then requested. For the analytical methods, it should be demonstrated, that these methods are basically applicable in the minor species. Also marker residues should exist in all species examined.

In accordance to the above mentioned Note for Guidance, the CVMP issued the Note for Guidance on the Establishment of Maximum Residue Limits for *Salmonidae* and other Fin Fish, EMEA/CVMP/153b/97 [26] taking into account, that only for a very few substances used as active substances in medicinal products for fish, MRLs have been established. In this Note for Guidance it is concluded that extrapolations to *Salmonidae* and other fin fish are acceptable when MRLs have been established for a substance in muscle in a major mammalian species and where certain data to support such extrapolation are provided. Also parent compounds are normally acceptable as a valid marker residue in *Salmonidae* and other fin fish.

Later on in 2000 also an approach for the extrapolation of existing MRLs from major species to additional species or even all food-producing animal, providing that there are similar MRLs established for tissues for the three major classes of species (ruminants, monogastrics and poultry) was established 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 [7]. Additionally certain requirements regarding the availability of analytical methods for these additional must be met. Following examples for an extrapolation are indicated in the Note for Guidance:

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

Table 1: Extrapolation of MRLs according to the Note for Guidance on the Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of Animal Origin [7].

Also in the Notice to applicants and Guideline Volume 8 [4] suggestions for extrapolation of MRLs are included. In contrast to 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 [7], the general extrapolation of major ruminants to all ruminants is restricted to meat only.

An extrapolation of MRLs derived from major species (cattle or sheep, pigs and chicken or poultry) also to fish is possible, if the parent substance is acceptable as marker residue for the MRL in muscle and skin.

In the Implementation of the Note for Guidance on Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of Animal Origin, EMEA/CVMP/069/02 [27], the CVMP reported that for 12 substances an “automatic” extrapolation had been recommended by the CVMP without formal applications. Further extrapolations would be possible only after an application has been filed.

In 2003 the European Commission published the “Reflection Paper on Residues in foodstuffs of animal origin” [28] where several Member States suggested to legally introduce an extrapolation procedure based on scientific principles. If the scientific data are insufficient to extrapolate to all species, the procedure should be flexible enough to restrict MRLs only to certain tissues or species. This would help to reduce the loss on veterinary medicinal products because of the required data for an MRL assessment for each target tissue and/or species.

In the Position Paper regarding availability of veterinary medicinal products – Extrapolation of MRLs, EMEA/CVMP/457/03 [39], the CVMP noted, that the efforts made so far are not sufficient, to overcome the availability problem of veterinary medicinal products for food producing animals. They suggested to assemble a list of substances for which MRLs should be established, which are considered essential for certain therapeutic indications in certain species for which no alternatives would be available. The substances in the list should have a generic status to avoid an exclusive marketing advantage for a specific company and the analytical methods should be available. The most critical availability problem is related to minor species, especially sheep and goats. For these two species products containing agents against ecto- and/or endoparasites and for the treatment of inflammatory diseases were identified. For other therapeutic groups an application for the extension of MRLs must be submitted including all requested scientific data. The CVMP also considers proposals for extrapolations for other urgently needed substances or species (e.g. from chicken to poultry).

If a new application for the establishment of MRLs for a new animal species the guideline on safety and residue data requirements for veterinary medicinal products intended for minor uses or minor species, EMEA/CVMP/SWP/66781/2005 [40] states that normally only a residue file is required, because the ADI is the same regardless of the indications. If the requirements of the above mentioned guideline and the Note for Guidance on the Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of Animal Origin [7] are fulfilled, the CVMP considers to carry out the assessment for such extrapolation based on a substantiated request without the payment of fees.

3.1.2. Modifications of the Regulation effected by the new Proposal

The proposed replacement of Council Regulation (EEC) No 2377/90” [6] on procedures to establish MRLs suggests “to make the assessment of possibilities for extrapolation a compulsory part of the overall scientific assessment and to create a legal basis for the Commission to lay down the principles for applying extrapolation”. The establishment of MRLs shall be part of the scientific risk assessments, leading to risk management recommendations. This risk assessment can be performed by independent experts. So no new data have to be provided and additional costs are avoided.

Article 5 of the new Regulation proposes to use:

- MRLs for substance/foodstuff for another food from same species, or
- MRLs for substance in one/more species for other species, or
- MRLs for substances/foodstuff for another foodstuff derived from other species.

So the new Regulation proposes to establish principles to extrapolate data on metabolism and residue distribution of pharmacologically active substances (MRLs) which have been set for a specific species to other species and/or foodstuffs, where an authorised product is not available.

At the first reading on the Commission proposal to Parliament and the Council (COM(2007)0194), texts adopted, 17.6.2008, P6_TA(2008)028 [41], the European parliament adopted the legislative resolution amending the proposal for a regulation of the European Parliament and of the Council laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, and repealing Regulation (EEC) No 2377/90. They proposed, that for the extrapolation between different animal species, a safety factor should be applied when setting maximum residue limits.

3.2. Alternative methods to establish an MRL

The establishment of an MRL resulting in a withdrawal period is a complex procedure in which a lot of points have to be considered. This complex procedure is mainly based on the establishment of the ADI. The basis for the calculation of the ADI is the NOEL.

The NOEL is established from a series of required toxicological studies and demonstrates where administration of a certain dose of a product has absolutely no effect on the animal, either clinically, toxicologically or biochemically. It is based on the kind application, a defined analytical method and a animal species or cell culture test system. So different methods may result in different NOELs. In certain cases the NOEL is also expressed as NOAEL or, the LOAEL.

The NOEL procedure was criticized mainly because of statistical reasons by several authors:

Leisenring [42] and Kaneene [43] criticised the NOAEL because of its sensitivity to sample size, insufficient dose-response relationship and its high sampling variability from experiment to experiment (statistical variation). Leisenring [42] stated that the NOAEL may be set at unacceptable high risk levels to ensure safety.

Laskowski [44] criticised that by using terms as “NOEL” there is a loss of information about the significance level of the test. He suggests to use a statement as “no significant difference was found at the 0.05 level”. Laskowski also argues that the aspect of variability is not examined. The responses of living organisms on environmental factors should follow the Gaussian distribution but there is always some fraction of a population (even if negligibly small beyond ±3 standard deviations) that is affected by any level of a particular environmental factor. He favours the regression analysis procedure as a powerful, flexible and robust method because it allows to estimate the effect level for any concentration as well as the concentration causing the effect level of interest, both with appropriate confidence intervals.

Kooijman [45] addresses several problems. His main point for criticism is that the NOEL or NOEC (no observed effect concentration) can be misleading because of the limited statistical properties. Like Laskowski he also argues that the aspect of variability is not examined. The results for the effect level and confidence interval are mainly dependent on the model chosen. For example the LC50/EC50 model has some amiable statistical properties, but it predicts that individuals are not affected by very high concentrations of very toxic substances, what is shown to be wrong based on experimental data. So it is not useful for a risk assessment.

Also Nelly van der Hoeven [46] states that the NOEL is used because of its simplicity, but it is missing a statistically significant effect.
In a second paper [47], she argues that the NOEC will be larger if the experiment is performed with less replicates or under less controlled conditions with a larger within replicate variance. For this reason information about the significance should be included, e.g. the minimum significant difference – MSD. The MSD is a test to distinguish between a treatment group and a control group and is only given for parametric tests based on a normal probability distribution (e.g. the Student's t-test). If no other methods are available, it also can be applied to non-parametric tests.

Wheeler [48] discusses three approaches to assess an MRL:

1. The reference dose (RfD) is calculated by taking the NOAEL divided by an uncertainty factor (UF). This method is mainly applicable for endpoints of substances that demonstrate threshold effects. For the UF normally a factor of 10 is applied to include the uncertainty in extrapolating from a LOAEL to a NOAEL, uncertainty when extrapolating from animal studies to human populations (interspecies extrapolation), uncertainty that populations vary within themselves (intraspecies variability) and that susceptible humans may not be adequately protected when using data averages from nonsensitive populations. This approach was criticized by Barnes [49] because it does not take the slope of the dose-response curve or sample size of a critical study into consideration.
2. The Physiologically based pharmacokinetic modelling (PBPK) is useful for route-to-route extrapolations and in reducing uncertainty when extrapolating from animal models to humans. The limitation of this model is that nonlinear functions are not reflected.
3. The Benchmark dose (BMD) is a statistical lower confidence limit for a dose that produces a predetermined change in response rate of an adverse effect compared to background. The MRL is then determined by dividing the BMD by an UF. The advantages in comparison to the NOAL approach are, that information about the slope of the dose-response curve are reflected. Also the number of animals and the corresponding confidence intervals are reflected in the BMD. Other advantages of this method are that dose extrapolations are possible and that for extrapolation from LOAEL to NOAEL no UF is needed. Mathematical modelling tools such as the benchmark dose offer alternative approaches to the traditional NOEL approach, but still require qualitatively similar dose–response data.

The NOEL refers to a given test result from a series of animals, so after a second test, the NOEL may be different. Because of this and other reasons there was an ISO resolution (ISO TC147/SC5/WG10 Antalya 3) as well as an OECD (Organisation for Economic Co-operation and Development) workshop recommendation [50] that the NOEC should be phased out from international standards.
Alternatives to the NOEL procedure were discussed by the OECD [51]. The main objective of this document was to provide practical guidance on how to analyse the observations from ecotoxicity tests and to develop new toxicity test guidelines by giving information on experimental design and statistical analysis issues.
One problem is that the NOEL (NOEC) is still required in many regulatory standards from many countries and the alteration of the study design is too costly to fulfil the requirements for regression models. Therefore guidance will be provided on the statistical methods for the determination of the NOEL (NOEC).

The NOEL is also criticized, because it is determined in animals (mostly rodents) and not in humans. The reliability of toxicity tests is limited by the number of animals tested. Such tests cannot represent the diversity of the human population, subgroups of which may show different sensitivities (e.g. children, old or ill people).

Also the ADI procedure was criticized:

Considerable research effort is put into developing the safety and residues documentations for veterinary medicines so that the ADI values can be calculated, MRLs set and withdrawal periods established. This process, together with residues monitoring to ensure that residues above the MRL do not occur and that prohibited drugs are not used, serves to ensure safety for the consumer, especially as large safety factors are built in at several stages of the process.

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.
There is a need for alternative approaches to the evaluation of veterinary drugs, particularly when it is not possible to set an ADI.

Also the JECFA has published 2004 on their web site a statistically based approach to establish MRLs for veterinary drugs and a calculation program with examples [52]. The approach is based on a linear regression analysis and statistical estimation of one-sided upper tolerance limits for the marker residue depletion in the individual target tissues. The residue intake based on the food basket is then calculated from different time points on the depletion curve. Finally the MRL is determined by comparing the calculated intake of residues with the ADI and the time point of depletion below the ADI.
This method would also fit the regulatory requirements of the US Food and Drug Administration (FDA).

This approach was commented by the EMEA in 2005 (EMEA/CVMP/SWP/367651/2005) [53]. The CVMP supports the statistical methods for the estimation of MRLs, even if it is different from the current practice as adopted by CVMP. For the JECFA approach the calculated withdrawal period is only valid for the specific product and dosing regimen used to generate the residue data and needs to be confirmed if other products are used. The calculated MRLs, once established, remain valid for other applications as well.

Differences between the methods of JECFA and CVMP can be expected mainly between the relative concentration of the MRL and the target tissues where noticeable. The JECFA method is limited in the statistical requirements for a linear regression analysis of all four target tissues and no statistically based approach allowing to calculate MRLs for milk or eggs is proposed.

Another aspect in the establishment of MRLs is information on residues at the injection site. Sanquer [54] criticizes this concept because in the guideline on injection site residues (EMEA/CVMP/542/03-FINAL) [55] the two reference thresholds are based on chronic studies. He also criticizes the statistical method used in this Guideline [56] relating to the residues at the injection site. Sanquer suggests to use the Acute Reference Dose (ARD) or Acceptable Single Dose Intake (ASDI). The MRL could be used when an active compound or its metabolites show an allergic potential.

Another aspect are methods for the estimation of withdrawal periods:

Three additional methods for the estimation of withdrawal periods of veterinary medicinal products in food producing animals were described by Vranic [57]:

1. **Decision Rule:** The withdrawal period is calculated by adding the time in which the residues in all tissues of all observed animals are below the MRL to a safety span,

which is dependent on study design, data quality and pharmacokinetic properties of the drug. This quick and simple method does not require stringent assumptions about the sample population. Only if observations above the MRL were observed, an additional group of animals have to be slaughtered to declare the withdrawal time. This procedure has to be repeated until there are no observations above the MRL. The main disadvantage of this method is the statistical inference because of the impossibility of assessing the uncertainty of the results.

2. **Linear regression:** The withdrawal period is settled as the time when the upper one-side tolerance limit (95% or 99%) with a given confidence (95%) is below the MRL. When departures from basic assumptions of the model are detected, other transformations (power within a family) might be considered.
3. **Non-parametric approach:** The withdrawal period is determined as the time when the residues of at least 95% of the animals is below the MRL. For this method all animals can be comprised in establishing the withdrawal period, even if the residues are below the LOD (limit of detection) and or LOQ (limit of quantitation) of the analytical method. The disadvantage of this method is that the slaughter times must be chosen during the declining phase of the residue kinetics because it is supposed that the percentage of individuals that have a concentration of residues above the MRL decreases with the time. So the sample size must be increased what also reduces the theoretical assumptions.

With two examples Vranic showed that the withdrawal period is shortest for method 2, increasing for method 1 and longest for method 3.

4. Discussion

The main goal of the legislation on veterinary medicinal products is to protect human and animal health and welfare and to harmonize these issues with trade requirements concerning residues of pharmacologically active substances in veterinary medicines for food producing animals.

The use of veterinary medicinal products in food-producing animals may result in the presence of residues in foodstuffs obtained from treated animals. Since January 2000 it is not allowed to use any active substances in veterinary medicinal products for food-producing animals unless the MRLs for the substances concerned have been included in Annex I, II or III of Regulation (EEC) No 2377/90 [2], as amended. The setting of MRLs ensures that consumers do not ingest potentially harmful residues. When establishing a MRL, consideration is also given to residues that occur in food of plant origin and/or come from the environment.

To establish an MRL for known substances, new residue trials, new metabolism studies, updated routine analytical methods, additional microbiological investigations as well as new pharmacological and toxicological studies are requested. The creation and assembling of these data is a time consuming and expensive process. Medicinal companies have to examine very well, if these expenses can be earned by future sales.

4.1. The MRL assessment process

The assessment process for the establishment of MRLs (resulting in the Summary Reports/EPMARs) was not substantially modified for more than 10 years. Comparing Reports from 1996 (e.g. Aminosidine [58]) and 2008 (e.g. European Public MRL Assessment Report (EPMAR) Gamithromycin Bovine species [59]) it can be recognized, that the same aspects (Pharmacodynamic and Pharmacokinetic properties, toxicology, ADI calculation, residues and marker residue) are included in both reports. In the recently prepared reports all aspects are described in much more detail. Also, not only the results of studies are presented, there is additional information on how the studies were conducted.

4.2. EU and Codex MRLs

Since 1992 MRLs are set by the European Commission or the Codex Alimentarius Commission. Before this time, they were set by each country individually or by the Codex. The proposed regulation [6] suggests to adopt Codex MRLs to save time and money, but several member countries are unwilling to implement Codex standards. They object that the Codex is not comprehensive enough to promote international harmonisation of food standards and that there is a lack of transparency in the Codex procedure. Also, there is no list of prohibited substances and drugs in use, which have no Codex ADI or MRL. Until know, MRLs strongly differ. In most cases the MRLs set by the EU are lower than those set by Codex.
Additionally there are differences between the geographical areas (EU – USA) which can be observed in the International Maximum Residue Limit Database / Veterinary Drug MRL Database [60].

In terms of harmonisation it is very important to adopt MRLs set by the Codex Alimentarius Commission as proposed by the new regulation [6]. In connection with the application for a marketing authorisation of a veterinary medicinal product for a food producing animal, it would be very advantageous to have the same MRLs in all countries/regions (EU, USA, Japan…). This would reduce development time and save a lot of resources (time and money).

4.3. Unacceptable residues in or on a food

The success of the current regulation concerning residues in food can be demonstrated by the data of the national residue control plan for food of animal origin which were collected in Germany since 1989. In the course of this program samples for residues of undesirable substances in e.g. meat, milk, eggs and honey have been examined. According to the German annual report 2007 for the national residue control plan [61] more than 50.000 samples were analyzed in 2007. More than 99% of these samples showed residues below the MRL. For cattle and swine only in 0.3% and for poultry only in 0.05% of the analyzed samples forbidden residues could be detected.

For substances in veterinary medicinal products without an MRL the “zero tolerance” policy applies to avoid any possible hazards to human health arising from residues in foodstuffs of animal origin following administration of veterinary medicinal products to food producing animals. Due to the fact that the analytical methods became more and more sensitive, residues were detected at ever lower levels. Moreover, different Member States detected the residues at differing concentrations. This resulted in a disharmonisation regarding the detection of residues in foodstuffs within the Member States of the EU without a clear scientific basis and led to barriers of the free movement of foodstuffs across borders.
In this context the CVMP stresses the need of a co-operation between the different Member States to ensure a harmonisation also in relation to establish ADIs and MRLs.

In some cases Member States detected unacceptable residues in or on a food. There are several reasons for the existence of these residues resulting from the treatment of a food producing animal:

- **Use of substances, which are not authorised for use in food producing animals in the EU**

  This is a problem which mainly occurs in food imported from countries outside of the EU. There also the controls are very limited. One discussed example is the import of shrimps from China, which sometimes contain traces of residues not authorised in the EU. Therefore RPAs are discussed as a pragmatic solution which may overcome this problem. RPAs will be set by the CRL and for the suitability of these RPAs a risk assessment will be performed by EFSA.

  Another problem is, that it is difficult to detect some substances by existing analytical methods which were used only in small amounts. Especially when mixtures of several illegal substance were used the detection of all substances is extremely difficult and time consuming. Here also the different Member States have to work together and share the development of improved analytical methods. They also should share laboratories for the analysis or e.g. build centres of competence for the analysis of residues.
  The analytical methods to detect residue limits which are used to determine a MRL have to be developed and validated. This is a time consuming and expensive process. Consequently, some veterinary drugs used for minor species have no MRLs and their

use is illegal. One possible solution may be strengthened controls and raised penalties (legal sanctions).

- **Drugs may be used to treat conditions and species for which they are not targeted**

  This may be caused by abuse and misuse but another reason is the reduced availability of veterinary medicinal products for food producing animals and especially for minor uses and minor species.
  If no authorized product exists for the treatment of a condition in a particular species and where it is necessary to avoid causing unnecessary pain or suffering, the cascade principle can be applied in accordance with article 10 and 11 of Directive 2001/82/EC, as amended [1]. A veterinary surgeon is permitted to use a veterinary medicine authorized in an EU member state or recourse to off-label use. In situations where there is no such veterinary medicine, he may use a medicinal product authorized for humans or a medicine prepared extemporaneously. In any case, the veterinary surgeons should also emphasize the importance of correct dosage and adhering to withdrawal periods.
  So the main responsibility for the veterinary surgeons is to decide which and how a veterinary medicinal product has to be used, but also the farmer has an appropriate responsibility to protect human and animal health and welfare.

- **Not considering the withdrawal period**

  Animals are send to slaughter and milk is delivered to the dairy without considering the withdrawal period. This may be by mistake, poor knowledge or consciously (mainly for financial reasons). To avoid this problem, the veterinary surgeon has the responsibility to ensure that the veterinary medicinal products are used according to the indication and that the farmer is informed to consider the withdrawal periods. However, the conscious action of farmers can't be avoided be these measures. Only strengthened controls and raised penalties (legal sanctions) may be a way to overcome this problem.

4.4. Main problem: Availability

The existing legislation on pharmacologically active substances used in veterinary medicinal products increased and ensures consumer protection but also significantly contributed to a progressive loss of many useful products and limited new product introductions for uses in food producing animals in the European Community.

The implementation of Regulation (EEC) No 2377/90 [2], as amended, which came into force 1992 had a strong impact on the availability of veterinary medicinal products and the control of residues of pharmacologically active substances that may be contained in veterinary medicinal products used in food producing animals [28, 62, 63].

After implementation of the regulation, the competent authorities realized that they carried the regulation to excess. The main arising problem is to ensure the availability of appropriate veterinary medicinal products for food producing animals. This problem became acute when at 1 January 2000 the transitional period ceased and since then, veterinary medicinal products containing pharmacologically active substances that are not listed in Annex I, II or III of Regulation (EEC) No 2377/90 [2], as amended, can not be authorised for food producing animals.
Also in the Position Paper regarding availability of veterinary medicinal products [39], the CVMP noted, that the efforts made so far are not sufficient, to overcome the availability problem of veterinary medicinal products for food producing animals.

The European Commission already proposed in December 1999 [64] to allow the use of veterinary medicinal products without MRLs in horses, provided that treatments are recorded in the equine passport and that those horses do not enter into the food-chain before 6 months after a treatment.

In 2004, the European Veterinary Medicines Directive was amended substantially in order to simplify and clarify the system of regulating the marketing and use of animal health products. In recent years only a limited number of new veterinary medicinal products for food-producing animals have been authorised. Also a Commission's public consultation highlighted, that the regulations were too complicated or inappropriate. The current practice of only limited use of extrapolating MRLs to other tissues and species without a fee had no great effects in recent years.

A reduced availability of appropriate veterinary medicinal products for a specific treatment for a specific species may contribute to the misuse or illegal use of substances.
With the experience gained, it has proved necessary that there is a urgent need for a broad review of the current legislation. The system of setting maximum residue limits has to be modified but the overall system for setting such limits should be maintained, to ensure human and animal health and welfare.

4.5. Proposals for a solution

The European Commission suggested [32] to review the existing regulation by incorporating specific legal provisions and amending existing rules.
A review provides the chance to overcome the existing problems on availability, residues, food imported from countries outside of the EU and simplification. This should result in improved compliance.

The main aims of the new regulation are, to:

- **Guarantee the availability of veterinary products for food producing animals**

  There are some suggestion (establish MRLs for substances intended for use under the “cascade” provision and for substances not intended for use in veterinary medicinal products - biocidal products (Article 9 of the revised MRL regulation in accordance with Article 3)), which may contribute to improve the current situation but most likely to a lower extend.

  It can be expected, that the current requirements of applications for establishing MRLs in preparation for submission of marketing-authorisation applications for new veterinary medicines for food producing animals will continue to remain the number of new substances developed for food producing species and especially minor species at a low level.

  This can be shown by the number of new MRL applications as well as for extensions / modifications/extrapolations of MRLs for the last three years:

Establishment of MRLs for new substances			
	2007	**2008**	**2009**
Submitted	**2**	**1**	**0**
Withdrawals	**0**	**0**	**0**
Positive Opinions[1]	**3**	**2**	**1**
Negative Opinions[2]	**0**	**1**	**0**

Table 2: Establishment of MRLs for new substances, modified from (CVMP Monthly Report of Application Procedures, Guidelines and Related Documents (03/2009)) [65]

Extensions / Modifications / Extrapolations of MRLs			
	2007	**2008**	**2009**
Submitted	**1**	**2**	**1**
Withdrawals	**0**	**0**	**0**
Positive Opinions[1]	**4**	**2**	**1**
Negative Opinions[2]	**0**	**0**	**0**
Extrapolations	**0**	**5**	**0**

Table 3: Extensions / Modifications / Extrapolations of MRLs, modified from (CVMP Monthly Report of Application Procedures, Guidelines and Related Documents (03/2009)) [65]

In their work programme [66], the EMEA made a forecast for 2009 for MRL applications, especially concerning the "cascade" and biocidal products:

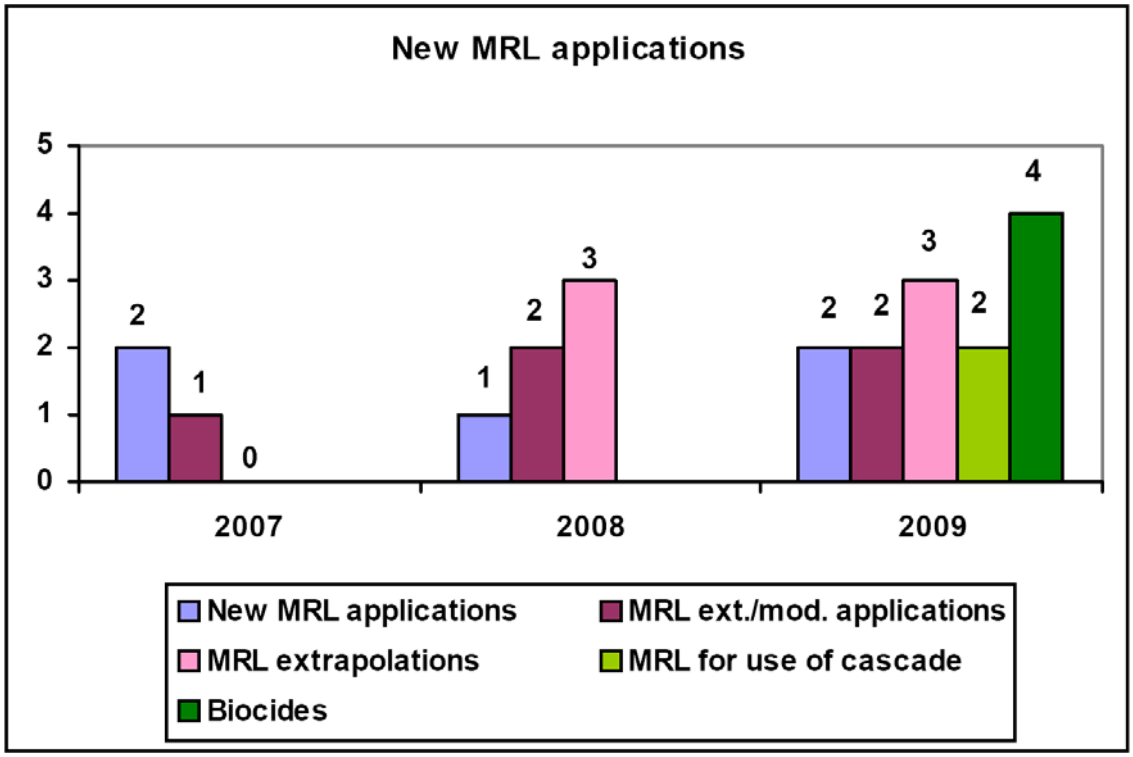

Figure 1: MRL applications (Work programme for the European Medicines Agency 2009 [66])

[1] Including opinions recommending definitive MRLs for substances with previously provisional maximum residue limits
[2] Including one opinion concluding that final MRL could not be established for a substance with provisional maximum residue limits previously established

The main two aspects to achieve this goal are the extrapolation of MRLs to other species and the adoption of Codex MRLs without a further risk assessment. These proposals can directly contribute to an improved availability because the pharmaceutical companies can directly apply for establishing MRLs and submission of marketing-authorisation applications for new veterinary medicines for food producing animals. Both proposals do not produce any further costs for the pharmaceutical companies and thus allow a faster return of investment.

- **Simplification and better regulation of the legislation.**

  The restructuring of the regulation and the integration of the MRLs into a single Annex will improve the readability. This is also an advantage for veterinary surgeons and the authorities, which only need to access to a single document. Further, the timelines for procedural management will be fixed. Therefore the proposal provides for significant improvements in terms of simplification and compliance. This will also contribute to avoiding duplication of work which reduces development time and cost for new products. Thereby simplification would also help to improve availability of veterinary medicine for certain animal species or conditions.

Also the CVMP supports that the current legislative framework on residues has to be reorganised to consider an impact on the availability of medicines. The Annex II concept should not be modified because Annex II substances are generally recognised as safe. Also the conduct of new studies to support the status of substances should be avoided.

The proposal for a new Regulation for MRLs of veterinary medicinal products in foodstuffs derived from animals seeks to simplify and harmonize existing legislation.

The European Parliament adopted a legislative resolution approving unamended, under the second reading of the codecision procedure of 2 April 2009 [67] and it is planned by the Commission to have the final draft adopted by late 2009.

4.6. Possible further improvements

There are further possibilities to improve the current legislation for veterinary medicinal products used for food producing animals and minor species. These suggestions may contribute to stimulate innovation and use the limited resources of both the regulatory agencies and commercial applicants more efficiently.

- **Expenses to meet regulatory requirements**

  A critical point in the course of developing new veterinary medicinal products for food producing animals are the costs of increasing regulatory requirements, especially the costs for the establishment of MRLs.
  The costs for the development of veterinary medicinal products are equivalent to human medicines, but the market size is only a fraction of that for human medicines. That makes it difficult to obtain a return of investment.

  Due to this fact, there is a lack of interest for Animal Health Companies, to generate new scientific studies and to develop veterinary medicinal products especially for Minor Use and Minor Species (MUMS), e.g. horses, goats, turkeys, rabbits or bees.

The economic aspect also contributed to the availability problem in the EU for food producing animals and minor species.

There is the need to differentiate between the legislations for human and veterinary medicines taking into account the different needs and market sizes of the two groups.

- **Data protection**

  As already discussed above, the development of a new medicinal product is a time consuming and expensive process. So, pharmaceutical companies have to calculate if there will be a sufficient return of investment.
  According to Article 14 of Regulation (EC) 726/2004 [68] and Article 13 of Directive 2004/28/EC [69], newly authorised veterinary medicinal products in principle benefit from a ten-year (8+2) period of market protection which can be elongated by one year for one or more new therapeutic indications with a significant clinical benefit in comparison with existing therapies.

  The data and market protection period recompenses the innovator and supports the need to recover the costs. On the one hand, this is a great benefit for the pharmaceutical industry, on the other hand, there is no incentive for competitor companies to develop new products for the same indication or to extend the marketing authorisations of existing products.

  Also the establishment of an MRL is time consuming and expensive, but the MRL is not protected at all. Once the substance has been included in Annex I, II or III of Regulation (EEC) No 2377/90 [2], as amended, any pharmaceutical company can cross-refer to the MRL or apply for marketing authorisations of veterinary medicinal products.
  Especially the high costs for the studies necessary to obtain a MRL and subsequently a marketing authorisation play a key role. Competitors who authorise a generic and who only refer to a MRL have no costs for the residue evaluation of the pharmacologically active substance contained therein. These companies have a much faster return on investment.
  It has been demonstrated, that the current (8 years data protection + 2 years market protection) system works well for innovations and this is a good hint that this system could also be adopted to MRLs.

  Another aspect are the analytical methods referred to in the MRL Summary Reports. These methods have been developed by the applicant and the EMEA is not allowed to publish these methods. So control laboratories in the EU have to develop their own methods to detect these substances. One the one hand, it's a waste of time and money to develop a method which is already existing, on the other hand, it is protecting the properties of the company who spend a lot of time and money to develop these methods.

  Also the Fédération Européenne de la Santé Animale (FEDESA) suggested to amend the MRL-Regulation in order to implement the principle of data protection: "FEDESA is convinced that the implementation of such a protection of intellectual property would improve the ability of companies to continuously improve old and develop new innovative products, increase product availability, enhance the wellbeing of animals and protect public health."

  Data protection for the innovator can be a useful tool to overcome the availability problem but it still needs a lot of discussion. For example there have to be clear definitions for which developments a data protection period can be gained and how long

this period should be. The establishment of an MRL for an additional species or tissue are innovations, which could qualify for an incentive.

Also the Data protection for sub-populations (e.g. calves, piglets and dairy cows) can be discussed. As an example medicinal products for paediatric use can serve (Data Protection according to Regulation (EC) No 1901/2006 [70]: for patented medicinal products: 6 months extension of the Supplementary Protection Certificate (SPC), for orphan medicines, 2 years of additional market exclusivity and for off- patent medicines: 10- years of market exclusivity).

But not only the establishment of an MRL should result in a period of data protection. Special attention should be drawn to minor indications and less economically important species, such as fish and bees for which only a limited number of companies are developing veterinary medicinal products. Here a elongated period of data protection (e.g. 13 years) could be granted.

Also the development of medicinal products for companion animals should not be disregarded. The companion animal health market is a fast growing market and incentives as data protection can help to guarantee the medicinal supply.

- **1-1-1 concept**

  Still under discussion is the 1-1-1 concept of IFAH-Europe (International Federation for Animal Health Europe), which means one dossier, one assessment and one decision for the marketing authorization for all veterinary medicinal product valid throughout Europe. This system is the continuation of the principle of mutual recognition for the creation of a true single EU market. The main objectives of the 1-1-1 concept [71] are:

  - Improve the level of public and animal health protection and contribute to a safe food supply.
  - Improve the availability of safe and efficacious veterinary medicines of appropriate high quality.
  - Provide a framework that stimulates innovation thus improving European competitiveness in line with the Lisbon Agenda.
  - Achieve Better Regulation and Simplification ensuring a fair and equitable regulatory environment proportionate to the needs of veterinary medicine sector
  - Ensure a more harmonised and practical implementation of the legislative objectives leading to predictable, efficient and proportionate regulatory procedures.
  - Realise the full potential of the common market via a radical re-think of the current regulatory system by all stakeholders starting from the 1-1-1 Concept
  - Reduce time and cost to market by 20% and reduce the cost of maintenance to 20% of the R&D budget.

  The aims of this concept are mainly in accordance with the aims of the current and proposed EU legislation but as already discussed it’s a moot question whether the recently suggested proposals for reforms of the EU regulatory system might be sufficient to overcome the current problems.

  This concept is a appropriate tool to avoid duplication of work for the competent authorities and the applicants and to have one single EU dossier for one single EU market instead of a time consuming and expensive series of national applications. This will reduce bureaucratic hurdles caused by national requirements. It is a efficient system

which will lead to a significant reductions in time and cost of product research and development and thus guarantee the availability of veterinary medicinal products throughout Europe.

- **Further simplification of the current legislation**

  There are further possibilities to simplify the current legislation which mainly challenges the local authorities and the EMEA.
  One aspect regarding the improvement of readability is to formulate the legislation more accurate. Especially the formulations in Guidelines could be improved to make clear conclusions. This will also help to improve compliance.

  Another approach is work sharing between authorities. Bureaucratic hurdles could be avoided and synergistic effects could be used. One the one hand, authorities can work together on the same projects, on the other hand a division of work is conceivable such as the formation of “centres of excellence” to deal with certain topics (e.g. assessment of MRL applications for antibiotics).

  Also the timelines for processing and authorisations could be accelerated. This could be reached by the already addressed principle of work sharing of authorities which can reduce the work load for the individual person or allows to focus on a specific topic, which also accelerates the work processes.

Combining the current legislation for veterinary medicinal products with the proposed concepts will help to guarantee international trade and the availability of safe and efficacious veterinary medicines, to protect both the health and welfare of animals and public health.

5. Conclusion

Regulation (EEC) No 2377/90 [2] as amended is laying down a Community procedure to evaluate the safety of residues of pharmacologically active substances. Based on this regulation, MRLs were set and withdrawal periods established. This process, together with the corresponding controls ensured, that residues above the MRL do not occur and that prohibited drugs are not used. In case of abuse or misuse legal sanctions were imposed.

The regulation contributed to protect human and animal health and welfare but it also had a strong impact on the availability of veterinary medicinal products. This was mainly caused by the requirements of establishing MRLs and the increasing regulatory requirements which are associated with high costs. Additionally the legislation was criticized because of the problems caused by the control of residues, food imported from countries outside of the EU, the difficulty to understand and the limited flexibility of veterinary surgeons in using or prescribing veterinary medicines.

Also the substantial amendment of the European Veterinary Medicines Directive in 2004 had no great effects regarding the availability problem.

Therefore in 2007, the European Commission suggested within an impact assessment [32] to review the existing regulation by incorporating specific legal provisions and amending existing rules.

The new proposal of the Commission with its 4 main objectives

- improve availability
- simplify the existing legislation
- provide clear references for the control of residues
- clarify the Community procedures establishing MRLs

should contribute to overcome the existing problems while keeping health protection as the over-riding objective.

The proposal to replace Regulation (EEC) No 2377/90 [2], as amended is a step in the right direction but it can be challenged, if the proposed measures will suffice to overcome the current problems, mainly the decreased availability of medicines for food producing animals in the Community.

The measures with the most promising effect may be the extrapolation of MRLs to other species and the adoption of Codex MRLs without a further risk assessment. These proposals do not produce any further costs for the pharmaceutical companies and thus directly contribute to the application for establishing MRLs and submission of marketing-authorisation applications for new veterinary medicines for food producing animals.

In spite of the measures proposed, it can be rather expected that the numbers of applications for MRLs and marketing-authorisation applications will continue to remain at a low level.

The question is if other suggestions like a data and market protection period would result in a much wider success to counteract the current availability problem because of the incentive for innovating pharmaceutical companies to obtaining a faster return of investment.

One open question is the supervision of the new legislation which may become quite complicated and perhaps uncontrollable without a massive increase of controls resulting also in a massive increase of expenses.

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Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

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