COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

Comments on the
Reflection Paper on Residues in foodstuffs of animal origin
prepared by the European Commission

The reflection paper states in its introduction that it presents points that need to be considered and debated with the view to reconsider and modify Community legislation concerning residues of veterinary medicinal products. The goal would be to determine new means to balance consumer protection, animal health, welfare and trade requirements concerning residues of pharmacologically active substances in veterinary medicines for food producing animals.

The document provides an analysis of the issues to be considered concerning the legislation to establish MRLs (Regulation 2377/90) in conjunction with the requirements laid down in the legislation on marketing authorisations (Directive 2001/82/EC) as well as the legislation and practical considerations regarding the residue control (Directives 96/23/EC 96/22/EC and Decision 2000/159/EC, as well as Decision 2002/657/EC). The document however does not disclose any directions for amendments to the current legislation envisaged by the Commission, what makes commenting particularly difficult.

The comments and proposals of the CVMP on the matter below will address the issues related to the establishment of MRLs and related points regarding residue control, while the residue control system as such is not commented on as this is not within the remit of the CVMP.

The CVMP appreciates the approach taken by the Commission in the reflection paper to consider the Community legislation concerning residues of veterinary medicinal products in its entirety.

1. Issues identified as problems in current scheme

The Commission considers as a major problem the lack of “reference points” for certain substances that would arise from the current regulatory system in the EU in relation to residues from veterinary medicinal products in food. Noting that MRLs or Annex II entries are often restricted to certain species or uses the Commission raises as a related problem that there would be no reference point in case of off-label or illegal use.

1.1 Substances in Annex II

As stated in the Reflection Paper as per definition of Annex II in Regulation 2377/90 no MRL was considered necessary for the substances concerned. The Commission also acknowledges that it would be not feasible for many Annex II substances to set MRLs due to various reasons.

The CVMP strongly supports the existing concept that MRLs do not need to be set for certain substances. The Annex II concept is a valid and well-established instrument for substances used in veterinary medicinal products for which it is not necessary for the protection of public health to establish a maximum residue limit and balances consumer protection, animal health and welfare.

Most of the substances in Annex II are substances that are generally recognised as safe, and can normally be used in all species and without any restrictions. Restrictions to certain uses, e.g. for specified administration routes, only for animals not producing milk or eggs for human consumption, or for certain species if e.g. residue data are only available for these species, are only recommended.
when scientifically justified. Not permitting restrictions for Annex II entries would require the need of many unnecessary animal studies and is not justifiable in respect to animal welfare and availability of medicines considerations, particularly if a veterinary medicinal product is intended for use only under certain restrictions. As, in general, applications for the establishment of MRLs are made only in respect of the intended use of a substance, there are in fact only few substances for which there is a need for any other type of use as now given in Annex II.

Where there is a need for a reference point regarding residue surveillance for Annex II substances, e.g. if there are concerns regarding illegal use, the relevant substances appear to be among those for which an ADI was established, but no MRLs were necessary to be established. For these substances the ADI could serve as basis for a reference limit for residues in tissues, if this would be required. The CVMP is willing to assist the Commission in establishing any such reference limits for substances that require residue controls.

1.2 Substances in Annex IV

The reflection paper raises as a main problem substances in Annex IV, which is understood as “zero tolerance”, that as a result any food contamination identified, even at the smallest concentration, would necessitate that the contaminated food would be considered unfit for human consumption. The recent Decision 2002/657/EC introducing Minimum Required Performance Limits (MRPLs) is intended to provide for a harmonised implementation of Directive 96/23/EC for chloramphenicol, nitrofuranes and medroxyprogesterone.

The CVMP noted that the problem of “zero tolerance” for forbidden substances does not only occur regarding Annex IV substances, but also regarding all substances that are prohibited under Directive 96/22/EC.

It is a logical consequence that where for a substance no safe levels can be scientifically established, and its use in veterinary medicinal products is therefore prohibited, in principle a “zero tolerance” approach should be applied. It is recognised that modern technology and methodology allow detection of very small concentrations, making apparent that this approach has in fact not been complied with in absolute terms. Setting administrative or technical limits such as the MRPLs is a practical way to deal with residue control requirements and to ensure consistent detection limits by all Member States. However, there is concern that establishing a scheme of administrative or technical limits for such substances would be misunderstood as “safe limits”, and that setting the limits could encourage continuation of the use of substances identified as hazardous. Furthermore, this system establishes double standards, strictly prohibiting use of Annex IV substances in the EU but accepting that they are used in third countries. The terminology used leading to an abbreviation similar to “MRL” contributes to the concern of misinterpreting the administrative levels as safe limits.

The need to harmonise the residue control in the EU for these substances is appreciated. However, establishing any kind of reference limits for residues in substances for substances, which are prohibited in the EU (both under Regulation 2377/90 and Directive 96/22/EC) should not be left solely within the competency of the Community reference laboratories and their MRPL approach but should be based on scientific approaches of assessing risk as well, whenever possible, and involving the responsible scientific EU committee. The possible approaches to achieve this should be explored. The scheme and approach to set any such reference limits should be transparent, and the system should allow that the values should be capable of being adapted in the light of scientific progress.

Another element regarding the current Annex IV substances to be considered is that in fact not all substances included in Annex IV have been placed there because of an established genotoxic potential for which it is, as a matter of principle, impossible to establish a safe threshold level. Several substances have been included in Annex IV because of a more or less strong suspicion of mutagenic/genotoxic action, which could not be refuted due to serious gaps in the scientific data. This means that there might also be safe threshold levels possible for some of these substances, but in absence of supporting data and applying the precautionary principle the substances were included in Annex IV. It should therefore be acknowledged that if new data would become available different conclusions could be reached.
1.3 Substances for which no conclusions of the assessments were possible due to the lack of data

The reflection paper identifies problems in respect to the control of residues of substances, for which no conclusions of the assessments were possible due to the lack of data, and that residues of these substances may be present in food due to their use in third countries from which the food would be imported, or due to illegal use.

In order to identify those substances from the list of substances concerned (see below) that are likely to cause residues in food, i.e. substances used for food production in third countries and those suspected to be used illegally, it seems appropriate to screen the list taking into account the use of the substances outside the EU. The substances identified could then be added to the control plans of EU Member States. In absence of MRLs however only a “zero-tolerance” approach would be possible.

It is recognised that it will be difficult to identify substances used in veterinary medicines in third countries from which the EU imports food. In the context of a discussion at the 14th Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) meeting in March 2003 on risk management methodologies including risk assessment policies in the CCRVDF it was suggested that a list of substances used in veterinary medicines in Codex countries be compiled by submitting national or regional lists. The aim was here to identify the substances for which no JECFA/Codex MRL exists. Such list would be of great help to identify any substances of concern in food from third countries. So far only few countries and the EU have submitted their MRL lists. This proposal should be reinforced by the EU delegations at the 15th CCRVDF meeting to be held in October 2004.

For substances which have been subject to a safety of residues evaluation in a third country the evaluation could be requested from this country and be reviewed in the EU as to whether the safe levels established by that country could serve as reference point for residue control in the EU.

The substances identified may also be candidates for Codex MRLs, provided that data allowing to establish MRLs can be provided. It is however recognised that it will be unlikely that such data would be provided by a company; it is noted that the CCRVDF currently explores possibilities to establish MRLs for priority substances without an applicant generating a dossier based on published data.

The CVMP is willing to support the Commission in dealing with issues arising from illegal use and crisis situations, in particular with respect to the establishment of short-term risk assessment for certain substances detected in imported food.

It appears useful that the list of substances, for which no conclusions of the assessments were possible due to the lack of data, would be communicated to the public. However, such publication is not considered necessary or appropriate as part of a piece of legislation, as the situation and consequences for these substances is similar to those, for which an application for the establishment of MRLs had never been made, and for which therefore a listing is not possible. The public EMEA document on the Status of MRL Procedures - MRL assessments in the context of Council Regulation (EEC) No 2377/90, which is periodically updated, lists the substances for which no conclusions were possible. The substances with withdrawn applications could be added.

Finally, the CVMP would like to comment on a minor point regarding the explanation in the description of the situation regarding the substances concerned. The reflection paper states on page 8, third paragraph from the bottom of the page, and on page 9, third paragraph (point 4) that the substances concerned relate to withdrawn applications. While for the majority of cases (56 substances) the applications were withdrawn, for a considerable number (in total 40 substances) the companies did however not withdraw their applications but did provide responses to the lists of questions. Nevertheless the CVMP was unable to make a recommendation for inclusion in any of the annexes due to the inadequacy of the data provided.
1.4 Substances, for which never an MRL application had been made
Substances known to be used in third countries or used illegally could be included in the residue control plans, if considered appropriate. The considerations outlined under point 1.3. apply similarly.

As for some of the substances concerned JECFA/Codex MRLs have been established these can then serve then as reference point. The EU policy regarding Codex MRLs for such substances appears to require review and possibly revision. This issue is further detailed below.

Codex MRLs
In absence of an MRL application and full dossier, the current practice is that the EU does not make qualified comments as to whether draft Codex MRLs for a substance which has not been evaluated in the EU can be supported or not, unless an assessment of e.g. similar substances would indicate concern. It appears appropriate that in future the CVMP should for such cases carry out an evaluation on basis of the JECFA reports, with the objective to make a recommendation for a qualified EU position on these substances.

A more general issue is the EU policy on how to deal with Codex MRLs once the Codex Commission has adopted them. In accordance with Regulation 2377/90 the CVMP takes account of any existing JECFA evaluation and Codex MRLs when evaluating an application for the establishment of MRLs for a substance, with the objective to agree on the same MRLs where possible. However, due to differences in the data available, but more importantly differences in the evaluation approach, and in order to ensure consistency within EU evaluations, sometimes the JECFA MRLs cannot be supported and eventually MRL values different from the Codex ones are established in the EU. Equally, if EU MRLs have already been set, but where JECFA/Codex agrees on different values, at the end a different set of MRLs exists for imports of food from third countries and for the control within the EU. While due to the margins of safety applied for most substances no consumer safety concern is expected to arise, this situation is considered not satisfactory. It also may provide for unfairness towards EU food producers vs. those from third countries. A clear EU policy regarding the implementation of Codex MRLs as to whether they become EU MRLs or not should be established. Adequate legal provisions or procedures for the implementation of Codex MRLs should be established.

1.5 Species specific MRLs/restriction of MRLs
The reflection paper somewhat criticises the fact that during the implementation of Regulation 2377/90 it evolved that MRLs are established for specified animal species and not for all food producing animals, and states that this would not be a provision of the Regulation. The move towards species specific MRLs was science based, as different kinetics and residue depletion were observed in different species. JECFA/Codex actually did establish species specific MRLs even earlier than CVMP.

Having completed the safety of residue assessment for old substances the CVMP however took on to review during the year 2000 all MRLs set by that time as to whether the approach of species specific MRLs can be relaxed and extrapolations to other species be undertaken without residue data in these species by ensuring consumer safety. The conclusions of the CVMP laid down in the Note for Guidance on the risk analysis approach for residues of veterinary medicinal products in food producing animals (EMEA/CVMP/187/00-FINAL) were that for the vast majority of substances the variation between species is small and MRLs can be extrapolated within a class of animals. If for several species that are specified in the abovementioned Note for Guidance the same or similar MRLs have been set, even the extrapolation of the MRLs to cover all food producing species is justified. Extrapolations of existing MRLs have been undertaken in this respect.

In summary, the CVMP confirms taking into account the analysis of data for over 100 substances for which MRLs have been set in the EU that in establishing these limits consideration needs to be given to the residue depletion in the different species, but that the degree of specificity as in some previous years is not necessary to ensure consumer safety.

As pointed out above under 1.1 for Annex II entries, restrictions to certain uses, e.g. only for animals not producing milk or eggs for human consumption, are scientifically justified, the reason being that in
absence of data concerning residues in the respective food commodities such as eggs and milk no MRLs can be set for these. Not allowing such restrictions would mean that in all cases, even if a therapeutic indication or mode of action defines the use of a substance to animals not producing milk or eggs for human consumption, data for the establishment of MRLs in these would have to be conducted. Otherwise these substances would be lost for treatment of animals entirely.

1.6 Analytical methods
Analytical confirmatory methods for the purpose of residue control submitted by applicant companies are provided by the EMEA to the Commission and Member States in accordance with Regulation 2377/90, as amended. The EMEA also provides voluntarily these methods to the Community Reference Laboratories (CRL). The provision of the methods to the CRLs appears to be a necessity and should be included in the revised legislation.

Experience has shown that the analytical methods provided by applicants within MRL applications are only used to a very limited extent by the reference laboratories. Normally the reference laboratories develop new analytical methods and the method provided by the applicant may be used only as a basis for this. It is therefore proposed that the analytical methods used for the residue depletion study and which was validated for that purpose, should be sufficient as basis for the method development by the reference laboratories.

Where there is a need for residue control regarding a substance not included in Annex I or III as discussed above, it may be useful to explore the possibility to use as basis for the development of an analytical method for the residue control the methods developed by the applicant companies and provided in the MRL application dossier for residue depletion studies.

2. Proposals for revised legislation
The Commission’s intention to better interconnect and streamline the relevant Community legislation and to remove and inconsistencies and to bring in line with principles of the Food Law (Regulation 178/2002) is appreciated. The CVMP stresses that the efforts for consistency should particular include also legislation and approaches regarding residues from use of feed additives, pesticides and biocides, where appropriate.

In this context the CVMP also stresses the need of a co-operation between the different scientific EU committees dealing with related matters on establishment of ADIs and establishment of MRLs in order to ensure consistency in approach and conclusions, and the revised legislative framework should include such provisions.

The CVMP also appreciates the comments regarding the need to meet the requirements according to Regulation 178/2002 towards the risk analysis approach, and notes that a separation of risk assessment from risk management particularly in relation to the criteria for including substances into Annex II would not have always been applied in the past. The CVMP, as mentioned above, considers the concept and criteria for inclusion into Annex II valid. Considerations such as to the intended or known use of a substance should be part of a risk evaluation. The CVMP is interested in discussing the subject matter further with the responsible Commission services, as regards an appropriate approach in the future. Such overall risk analysis approach might also include the establishment of additional risk management considerations or “other legitimate factors” in relation to control measures for certain substances included in Annex II of Regulation 2377/90.

The CVMP proposes that some feedback mechanism be established in respect to the outcome of residue control by Member States through the Commission and the analytical methods developed for residue control by the NRLs and CRLs. The publication of the results of the residue control in Member States at EU level would be desirable. Furthermore, the ownership of official analytical methods for residue control should be clarified. The EMEA receives frequently correspondence from control laboratories in the EU, but particularly in third countries, requesting for provision of the analytical methods referred to in the MRL Summary Reports. As these methods have been developed by the applicant companies for MRL applications, they have to be treated as proprietary information and cannot be released to third parties. Industry so far stressed the importance of the ownership of the
methods considering that there would be no proprietary rights for MRLs, and other companies could use the published MRL Summary Reports for a marketing authorisation instead of generating own data.

The CVMP would like to offer some comments regarding the criticism that Regulation 2377/90 would be too inflexible as requiring final classification, and the Commission’s considerations that there are no procedures that would allow authorities to establish limits as a precautionary measure or for import purposes only, in which context the proposal is made to allow for an extended application of provisional MRLs. The paper states before that Article 6 of Regulation 2002/178/EC establishes that risk management shall take the precautionary principle into account when establishing measures. With respect to the evaluation of residues according to Regulation 2377/90 the only option to appreciate this principle would be the establishment of provisional maximum residue limits. At present such provisional MRLs may only be instituted for a period of maximum seven years. This proposal appears to provide for double standards: A full scientific evaluation and scientific dossier for substances used for producing food in the EU, and provisional MRLs for possible more than 7 years on basis for incomplete data while “scientific uncertainty persists” for substances used to produce food in third countries for import in the EU. Considering the amount of food imports, this appears a public health concern and not within the spirit of “provisional risk management measures” in application of the precautionary principle according to Article 6 of Regulation 2002/178/EC.

The CVMP also reflected on the Commission’s considerations of a future reorganisation and amendment of Annexes to Regulation 2377/90. While no indications of the direction of these considerations are given, the CVMP believes that a reorganisation regarding Annex II would be useful. In accordance with the considerations above in section 1.1 of this document Annex II could be reorganised to comprise the categories a) substances generally recognised as safe, b) substances with an ADI (that can serve as basis for a reference point), and c) substances with restrictions of use. Other existing categories such as substances of vegetable origin or substances used in homeopathic veterinary medicinal products could possibly be combined. One other, possibly more user-friendly option, to consider might be to drop the differentiation into different Annexes altogether and list the substances with their MRLs, or MRL status respectively, in alphabetic order.

The CVMP recommends stating in the revised Regulation that the MRL classification should be considered in conjunction with the MRL Summary Report for the substance, species and use concerned.

The CVMP supports that changes in the legislative framework on residues and any reorganisation and amendments of the annexes should consider the impact on the availability of medicines; in particular it should not result in companies having to conduct new studies to support the status of substances in Annex I or II.

The CVMP also supports that a revised legislation should recognise the fact of certain restrictions of MRL entries as discussed under point 1.1 and 1.5 and provide for a procedure for the extension/extrapolation and modification of MRLs.

In reflecting on the future legislative framework, it should be borne in mind that the residue control strategy is but one of several risk management strategies. Others comprise the particular obligations for veterinary medicinal products for use in food producing animals under the marketing authorisation legislation and the auditing of the implementation of the Commission’s residue plan.

3.  **Risk communication**

It is considered important that further efforts are made to improve communication, in an appropriate and comprehensive manner, to the users of veterinary medicinal products in respect to scheme of setting MRLs, its purpose, context within the marketing authorisation and residue control scheme, and impact. This is of particular importance regarding food imports from developing countries, where often due to insufficient knowledge on the toxicity of substances and lack of instructions of appropriate use, undesired residues have arisen. The EMEA is willing to contribute actively in such exercise.