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REPORT FROM THE COMMISSION TO THE COUNCIL
AND THE EUROPEAN PARLIAMENT ON THE OPERATION
OF THE COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

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1. INTRODUCTION

The Committee for Veterinary Medicinal Products was established by Article 16 of Directive 81/851/EEC on the approximation of laws of the Member States relating to veterinary medicinal products* in order to facilitate the adoption of common positions by Member States with regard to the granting of marketing authorizations by Member States for veterinary medicinal products. The Committee may also examine any question concerning the application of Directive 81/852/EEC relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of veterinary medicinal products.

In particular, the Committee is responsible for preparing advisory opinions on applications for marketing authorization which are submitted using the two special Community procedures, the so called "Multi-State" procedure established by Directive 81/851/EEC itself, and the "Concertation Procedure" which was subsequently established by Directive 87/22/EEC. In addition, as the sole advisory Committee of officials from Member States established at Community level with responsibilities relating specifically to veterinary medicines, the Committee also has to advise the Commission and Member States on more general aspects relating to veterinary medicines.

In accordance with Article 23 of Directive 81/851/EEC, the Commission is required to report periodically on the activities of the Committee. A first general report on the work of the Committee was included in the explanatory memorandum of the package of three White Paper proposals for the amendment of the veterinary medicines directives (COM (88) 779 final), which have now been adopted by the Council. This second report is intended to provide a more detailed account of the activities of the Committee up to the end of 1990. Further reports will be produced at annual intervals.

* A complete list of the Community Directives relating to veterinary medicinal products is set out in Annex 1.

On 15 November 1990, the Commission formally presented to Council a package of four proposals for the future system for the free circulation of medicinal products, for human and veterinary use, within the European Community, including proposals for the establishment of a European Medicines Evaluation Agency and new centralised and decentralised Community authorization procedures (COM (90) 283 final; O.J. N° C 330, 31.12.1990, pp 1-32). It is hoped that the present report, which describes the experience so far acquired within the CVMP, will serve as the basis for the informed discussion of these proposals as they relate to veterinary medicinal products.

2. ACTIVITIES OF THE CVMP

2.1 Membership of the Committee

In accordance with Article 16 of Directive 81/851/EEC and the Rules of Procedure adopted by the Committee (III/1267/83 Rev 2), the Committee consists of one representative from each Member State and one representative from the Commission, appointed for a term of three years, renewable. A list of the current members, who are all national officials responsible for advising on matters relating to the authorization of veterinary medicines in their home countries, is set out in Annex 2.

The Committee elects its chairman from among its members by absolute majority and secret ballot. The term of office of the chairman is three years, renewable once only. Following the promotion of Professor Arpad Somogyi to new responsibilities within the Bundesgesundheitsamt, Mr Jacques Boisseau, Director of the Laboratoire National des Médicaments Vétérinaires (CNEVA) at Fougères in France was elected chairman of the Committee in September 1988.

The rules of procedure also provide for two deputy chairmen, one of whom is elected by the Committee in accordance with the same procedure as the chairman, and who replaces the chairman in case of absence. The other is appointed by the Commission to transact routine business on behalf of the Committee between meetings. In September 1988, Mr Alastair Kidd, Deputy Director of the Veterinary Medicines Directorate at Weybridge, was elected deputy chairman, while Mr Fernand Sauer, head of the pharmaceuticals unit within the Directorate general for Internal Market and Industrial Affairs, continues to serve as the deputy chairman appointed by the Commission.

2.2 Communication and Information

The work of the CVMP is of pivotal importance in the application of the Community directives relating to veterinary medicines. Equally, the views of the Committee are of considerable interest and relevance to the industry, and to others with interests in this sector. In these circumstances, the Committee has decided to aim for the greatest possible transparency in respect of its work, subject only to the constraints imposed by the need to protect the confidential information submitted by companies in their dossiers for applications for marketing authorization.

There are three main aspects to this policy of transparency:

1. The adoption of a press release at the end of each meeting.
2. The presentation of an annual report on the activities of the Committee.
3. The organization of periodic meetings between the Committee and all groups interested in the authorization and control of veterinary medicines, including manufacturers, consumers, the veterinary and pharmacy professions, farmers groups, etc. It is hoped to organise the first such meeting in the course of 1991.

In addition, active consideration is being given to the possible admission of observers from consumer groups and industry to those parts of the meetings of the CVMP which are concerned with questions of general principle;

The Commission and the Committee hope that this policy of transparency will contribute to a greater public awareness and understanding of the processes by which veterinary medicines are evaluated and authorized within the Community.

2.3 Harmonization of scientific requirements

The authorization of veterinary medicinal products in the Community depends upon the applicant providing convincing demonstration of the quality, the safety and the efficacy of the veterinary medicinal product concerned.

Quality covers the verification of the ability of the applicant to produce a stable and homogenous product, in accordance with its approved specifications, on an industrial scale.

Safety currently covers three aspects:

- the safety of any residues of the product for human consumers of foodstuffs of animal origin;
- the safety of the product in the target species of animal;
- the safety of the product for the animal holder and the veterinarian.

Moreover, following the entry into force on 1 January 1992 of Directive 90/676/EEC, which amends the basic Directive, 81/851/EEC, consideration will also have to be given to the safety of the product for the environment.

Efficacy covers the verification that the product does indeed have the effects claimed by the manufacturer, for example, for the prevention or treatment of disease, or for the increase in growth or yields from the treated animal. In addition, in the case of a product intended to increase growth or yields, the efficacy criterion extends to the verification of the quality of the foodstuffs obtained from treated animals.

Directive 81/852/EEC as amended by Directive 87/20/EEC sets out the detailed requirements for the analytical, pharmaco-toxicological and clinical tests and trials which have to be conducted before authorization can be obtained for a veterinary medicinal product.

With effect from 1 July 1987, the Council has delegated to the Commission the power to amend the testing requirements set out in Directive 81/852/EEC. Moreover, following the adoption on 13 December 1990 of Directive 90/677/EEC extending the scope of the veterinary medicines directives to immunological veterinary medicinal products, the Commission also has to prepare new requirements for the testing of immunologicals.

A comprehensive review of the testing requirements for all categories of veterinary medicines is therefore being undertaken by the Commission in close cooperation with the CVMP and its various working parties. It is anticipated that draft texts will be available for consultation during the course of 1991.

In addition, the working parties of the CVMP are currently preparing a series of guidelines to complement the detailed legislative rules. Further information is given in section 2.5 below.

2.4 Standard application dossier

In order to progress towards the free movement of veterinary medicinal products within the Community, it is important to supplement the detailed work being undertaken on the harmonization of legislative requirements by action of an administrative nature which ensures that the same application dossier is acceptable to all Member States. A first step in this direction was taken with the publication of a "Notice to Applicants" in 1989 which, in addition to providing guidance on the use of the two Community authorization procedures, contains the basic structure of a harmonized standard Community application for authorization for veterinary medicinal products. This notice to applicants is published in Volume V of "The Rules Governing Medicinal Products in the European Community", which contains the rules currently in force for veterinary medicinal products (Catalogue Number CB-55-89-972-EN).

A detailed review of the "Notice to Applicants" will be required during 1991 to take account of the changes in the legal requirements for the testing of veterinary medicines and the entry into force of the reformed "Multi-State" procedure.

2.5 Working Parties of the CVMP

In order to provide specialist support in a number of priority scientific areas, the CVMP has established a number of working parties; safety of residues (1984); efficacy of veterinary medicines (1988); veterinary pharmacovigilance (1989); immunological veterinary medicinal products (1990). These working parties constitute an integral part of the CVMP and serve both to reinforce the expertise available to the Committee and to integrate a wide range of national experts into Community activities.

One of the major tasks of the working parties is the preparation of guidelines which provide detailed but flexible guidance for the industry on the conduct of the various tests and trials necessary to obtain authorization for a veterinary medicinal product. Although these guidelines are not binding, compliance with them provides the industry with a guarantee that the results of the various studies will be accepted as valid by the regulatory authorities of the 12 Member States.

2.5.1 Working party on the safety of residues

The working party on the safety of residues has been chaired by Dr Dieter Arnold of the Bundesgesundheitsamt since September 1988. The working party has responsibility for advising the CVMP on general principles for the safety evaluation of residues of veterinary medicines in foodstuffs of animal origin.

A comprehensive draft guideline on the safety evaluation of new veterinary medicinal products, with particular emphasis on the evaluation of the safety of residues was circulated to interested parties for comments during 1990, and after consideration of the comments received, is expected to be definitively adopted in the course of 1991. (III/3897/88)

In addition, the working party has responsibility for undertaking the evaluation of the safety of individual compounds which are authorized for use in food producing animals within the Community, and in preparing recommendations for maximum residue limits (MRLs) in respect of the compounds concerned, taking into account evaluations which may have been undertaken by the Codex Alimentarius. This important aspect of the work of the CVMP is described in detail in section 5 below.

2.5.2 Working Party on the Efficacy of Veterinary Medicines

The working party on efficacy, which is chaired by Mr Alastair Kidd from the United Kingdom, is responsible for preparing guidelines on the demonstration of the efficacy of veterinary medicines. During 1990, seven guidelines were sent out for consultation covering;

- general principles for the demonstration of efficacy and the conduct of clinical trials;
- preparation of veterinary clinical expert reports;
- fixed combination products;
- the demonstration of secondary pharmacodynamic actions;
- antimicrobials;
- anthelmintics for the bovine and ovine species;
- performance enhancers.

In addition, a number of other guidelines are at various stages of preparation, and are expected to be released for comment during 1991, including

- conduct of pharmacokinetic studies;
- conduct of bioequivalence studies;
- drugs acting on the central nervous system;
- efficacy of sedatives and hypnotics;
- efficacy of products for use in farmed fish;
- glucocorticoids and non-steroidal anti-inflammatory compounds;
- products for use in minor species;
- anthelmintics for use in species other than the bovine or ovine;
- intra-mammary preparations for the treatment of clinical and sub-clinical mastitis in cattle;
- teat dips for the prevention of mastitis in lactating cows;
- products intended to treat *Varroa Jacobsoni* and *Acarapis Woodi Parasitosis* in bees
- products for zootechnical purposes
- anti-coccidials for the treatment of coccidiosis in chickens

2.5.3 Working party on veterinary pharmacovigilance

The term pharmacovigilance covers the collection and evaluation of reports of adverse drug reactions to medicinal products and the adoption of appropriate regulatory action in response. Although pharmacovigilance in the human medicines sector is a well established activity, in the veterinary medicines sector, it is a relatively new area of activity.

The working party on veterinary pharmacovigilance has three major objectives;

- to agree a common methodology for the collection and evaluation of adverse reactions to veterinary medicines in animals among the Member States which already have a national pharmacovigilance system (currently Germany, France, Ireland, Italy and the United Kingdom)
- to provide technical advice and assistance for any other Member State wishing to establish such a system;
- to provide a forum for the exchange of information and discussion of specific problems concerning adverse reactions to particular products.

Up to the end of 1990, the working party was chaired by Dr Rinette Julicher of the Netherlands.

One of the first actions of the new working party was to create a Community wide rapid alert system for the exchange of information about urgent pharmacovigilance actions. The group is also preparing a comprehensive framework for cooperation at Community level in this area and a guideline setting out the responsibilities of the industry for the collection, evaluation and reporting of information about adverse reactions to veterinary medicines.

2.5.4 Working party on immunological veterinary medicinal products

In anticipation of the decision by the Council to extend the scope of the veterinary medicines directives to cover vaccines and sera, the CVMP decided to set up a specific working party on immunological veterinary medicinal products.

Currently chaired by Professor Leunen, from Belgium, this working party brings together experts on all aspects of the evaluation of veterinary vaccines. The working party has three main functions;

- the evaluation of individual applications for marketing authorization for immunological veterinary medicinal products derived from biotechnology, which are already being submitted in accordance with Directive 87/22/EEC;
- advising the Commission on the detailed test requirements necessary to show the quality, safety or efficacy of veterinary immunologicals;
- preparing general guidelines on the structure of the application dossier for this type of product and the conduct of the various tests and trials.

2.6 Quality of Veterinary Medicinal Products

The requirements for the quality of veterinary medicinal products, which are set out in Part I of the Annex to Directive 81/852/EEC, are substantially the same as the quality requirements for medicinal products for human use, as set out in Directive 75/318/EEC. For this reason, the CVMP has decided not to establish a separate working party on the quality of veterinary medicines.

However in March 1990, the CVMP held a special ad hoc meeting on the quality of veterinary medicinal products to consider subsequent developments in the quality requirements for human medicine and their relevance to the veterinary sector. In principle, the Committee agreed that the quality requirements set out in the notice to applicants for medicinal products for human use concerning the presentation of Part II of the Dossier and the Quality expert report were applicable to veterinary medicines with only minor detailed amendments. (See the Rules Governing Medicinal products in the European Community, Volume II, Catalogue N° CB-55-89-293-EN-C).

In addition, the Committee agreed that the following quality guidelines established by the Committee for Proprietary Medicinal Products could in principle be applied to veterinary medicinal products;

- development pharmaceuticals and process validation
- chemistry of active ingredients;
- stability tests on active ingredients and finished products;
- quality of herbal remedies;
- analytical validation.

The Committee has also subsequently agreed that the European Drug Master File procedure established for medicinal products for human use will be applied by Member States in the same way to veterinary medicinal products.

However, the Committee has decided to elaborate a separate guideline on the quality requirements for medicinal premixes intended for use in the subsequent manufacture of medicated feedingstuffs.

2.7 Good manufacturing practices for veterinary medicinal products

Following the entry into force of Directive 90/676/EEC, all production of veterinary medicinal products will have to be undertaken in accordance with the principles of Good Manufacturing Practices (GMPs). The Council has delegated to the Commission, in accordance with the so-called 'regulatory committee procedure', the power to adopt the principles and guidelines of good manufacturing practices which must be complied with.

In preparation for the entry into force of these new requirements, the Committee has undertaken a survey of the arrangements within Member States for the inspection of manufacturers of veterinary medicinal products. It emerged that the arrangements for the inspection and control of manufacturers of veterinary medicines were in most Member states the same as the arrangements for the control of medicinal products for human use. As a consequence of that survey, it was agreed that it would not be appropriate to prepare a special Community code of good manufacturing practices for veterinary medicinal products. Instead, the EEC guide to Good Manufacturing Practices (Volume IV of the Rules Governing Medicinal Products within the European Community) will be completed by two further annexes setting out the specific requirements for GMPs for

veterinary medicinal products and for immunological veterinary medicinal products. These two annexes are being prepared jointly by the CVMP and the Commission Working Party of Pharmaceutical Inspectors, and will be circulated for comments shortly, together with the text of the Draft Directive setting out the principles of GMPs for the manufacture of veterinary medicinal products.

2.8 Review of old veterinary medicines

In accordance with Article 52 of Directive 81/851/EEC, the Member States are required to apply progressively the requirements laid down in Directives 81/851/EEC and 81/852/EEC to old veterinary medicinal products which were first placed on the market by virtue of earlier provisions. This review should be completed before 1 October 1991.

In order to verify the progress of the review, the Committee has conducted a pilot questionnaire on the outcome of the review in the case of antibiotics of the tetracycline group. The Committee has now decided to conduct a more wide-ranging exercise covering a number of other widely used compounds.

In addition, the Committee has established a network of informal bilateral contact points in the Member States who are able to answer questions from the other Member States about the status and outcome of the review in specific cases.

Moreover, in accordance with Articles 20 and 22 of Directive 81/851/EEC, it is possible to refer specific cases for examination by the Committee, in particular where Member States have adopted divergent decisions as a result of the review. However, this possibility has not yet been used.

2.9 Hormones

In accordance with Article 3(a) of Directive 88/146/EEC, the CVMP adopted an opinion on a list of products containing oestradiol 17 β , testosterone and progesterone which may be authorized by Member States for the therapeutic treatment of a fertility problem in individual farm animals on 10 September 1987, which was subsequently transmitted by the Commission to the Permanent Veterinary Committee for consideration.

In addition, in accordance with Article 2(1)(b) of Directive 88/299/EEC, the CVMP is required to give a further opinion on a list of products containing hormonal compounds which may be authorized by Member States in view of the synchronization of oestrus, the interruption of unwanted pregnancy and the preparation of donors and recipients for artificial insemination.

The preparation of this second opinion was entrusted to an ad hoc working party chaired by Dr Cyril O' Sullivan from Ireland. Following consultation with Member States and the companies concerned, in January 1991 the Committee adopted its opinion, which will shortly be transmitted to the Permanent Veterinary Committee (III/3860/90 final).

3. THE MULTI-STATE PROCEDURE

The Multi-State procedure was established by Chapter IV of Directive 81/851/EEC. It enables a company which has obtained authorization for a veterinary medicinal product in one Member State to seek the extension of that authorization to at least five of the other Member States, using a procedure which is based upon the concept of mutual recognition of national marketing authorizations.

Upon receipt of a valid application, the five or more Member states concerned have 120 days either to accept the initial authorization or to put forward a reasoned objection explaining why authorization cannot be granted.

If objections are received, the Committee then has a further period of 60 days to give an opinion on whether or not the product satisfies the requirements for authorization laid down in Directives 81/851/EEC and 81/852/EEC. This opinion is not binding on Member States, but within a further period of 30 days, the Member States must indicate what action they intend to take on the opinion of the Committee.

In principle, this procedure offers a number of advantages to a company which wishes to place a product on the market of the majority of the Member States, in particular the use of a single common file for all Member States concerned, the simplification of administrative and linguistic requirements and strict respect for time limits during the evaluation of applications.

However, in practice the procedure has been rarely used. The CVMP has given an opinion on one application, for a product originally authorized by France, which concerned all eleven of the other Member States. Although certain administrative difficulties arose during the consideration of the application, which concerned one Member State in particular, the CVMP adopted a favourable opinion on the application in March 1988, and the product has subsequently been authorized by all eleven Member States. At the present time a further five applications are pending, and should be the subject of an opinion of the Committee during 1991.

In the course of 1990, the Committee undertook a detailed review of the "Multi-State" procedure and introduced a number of administrative changes. The new guidance for the use of the procedure is set out in Annex 3.

Following the adoption of Directive 90/676/EEC, further changes will be made to the procedure from 1992 onwards, in particular the reduction of the threshold number of Member States from five to two and the introduction of a right to a hearing for companies using the procedure.

It must be hoped that as a result of these various changes, the procedure will prove attractive to the industry and that a sufficient number of dossiers will be received to test seriously the feasibility of the 'mutual recognition' approach as an option for the future arrangements for the authorization of veterinary medicines within the Community.

4. THE CONCERTATION PROCEDURE

4.1 Scope of the concertation procedure

The legal rules governing the special Community procedure are set out in Council Directive 87/22/EEC. The objective of the procedure is to enable questions relating to the quality, safety and efficacy of medicinal products developed by means of new biotechnology processes and other high technology medicinal products to be resolved at Community level within the CVMP before any national decision is reached concerning a marketing authorization.

The concertation procedure is obligatory for all medicinal products developed by means of the following biotechnological processes (List A of the Annex of Directive 87/22/EEC):

- recombinant DNA technology
- controlled expression of genes coding for biologically active proteins in prokaryots and eukaryots, including transformed mammalian cells
- hybridoma and monoclonal antibody methods

In particular, it should be noted that although harmonized Community rules for immunological veterinary medicinal products have not yet entered into force, applications for immunological veterinary medicinal products produced using the above biotechnological processes must be referred to the Committee for an opinion in accordance with Directive 87/22/EEC.

During 1990 some uncertainty arose about the scope of application of List A in the case of certain techniques used in the manufacture of immunological veterinary medicinal products. The CVMP is currently preparing detailed guidance on the interpretation and application of list A to gene deletion techniques and the use of hybridoma and monoclonal antibodies for selection and purification of vaccine strains or of the finished product. In the meantime, companies considering submission of applications for such products are advised to contact the regulatory authorities of the Member States at an early stage to determine whether a reference to the CVMP will be required.

In addition, applicants for marketing authorization for the following groups of products may request that the application be considered under the concertation procedure (List B of the Annex of Directive 87/22/EEC):

- medicinal products developed by other biotechnological processes which constitute a significant innovation;
- medicinal products administered by means of new delivery systems which constitute a significant innovation;
- medicinal products containing a new substance or an entirely new indication which is of significant therapeutic interest;
- new medicinal products based on radio-isotopes which are of significant therapeutic interest;
- medicinal products the manufacture of which employs processes which demonstrate a significant technical advance such as 2-dimensional electro-phoresis under micro-gravity.

The timetable for the concertation procedure is based on the requirements of Article 8 of Directive 81/851/EEC. Since the applications relate to complex processes which are deemed to be exceptional, the rapporteur, in establishing the period for review, usually extends the time period of 120 days to include the additional 90 days provided for in exceptional cases by the directive.

4.2 Evaluation of applications within the CVMP

The initial evaluation of an application is undertaken by the rapporteur Member State. The assessment report of the rapporteur is circulated to all Member States, who make their own comments and add any further questions. The Committee then discusses all the questions and comments received and prepares a complete list of questions which is presented to the company. At this point the clock stops until the company has presented a single consolidated response to all the questions raised.

Thereafter, the rapporteur prepares a second updated assessment report which is again circulated to all Member States for comment, and discussed by the Committee. If the Committee considers that the company has presented satisfactory replies to all the questions, it will then adopt a favourable opinion. However, if the replies are considered unsatisfactory, the Committee identifies a list

of outstanding problems and the company is given a final opportunity to respond, either in writing or at a hearing, before the Committee adopts its opinion.

The opinion of the Committee is not binding, but Member States are obliged to inform the Committee within 30 days of what action they have taken on the opinion.

4.3 Use and outcome of the concertation procedure

Since Directive 87/22/EEC entered into force on 1 July 1987, a total of 8 applications have been received under the concertation procedure, six of which have concerned immunological veterinary medicinal products derived using biotechnological processes and two have been for products containing recombinant bovine somatotropin (BST).

Applications for immunological products are systematically referred to the immunologicals working party for advice before their consideration by the full Committee. Other applications under the concertation procedure are treated by the CVMP itself, although if necessary an ad hoc specialist working party may be set up to provide advice on specific questions.

To date, the Committee has adopted opinions in respect of three applications and five remain pending. The three opinions, all of which were favourable, concern the following immunological veterinary medicinal products:

- TOLVID, from the Upjohn Company; opinion adopted on 30 June 1989 but subsequently withdrawn, following the withdrawal of the application by the company in all 12 Member states;
- NOBI-VAC AUJESZKY, from the Intervet Company; opinion adopted on 28 November 1990;
- NOBI-PORVAC AUJESZKY LIVE, from the Intervet Company, opinion adopted on 28 November 1990.

The examination of the two separate applications concerning bovine somatotropin from Eli Lilly and Monsanto has presented a particular challenge to the Committee, partly because of the sheer volume of data submitted in support of the applications, and partly because of the difficulty in reconciling the legitimate requests for public information about these products with the constraints imposed by the requirements of commercial confidentiality. In order to respond to the latter concerns, the Committee has decided that once its evaluation is complete it will request the Commission to publish the opinion on each of these applications and it will also prepare a more detailed assessment report on each of the products concerned.

4.4 Hearings

Directive 87/22/EEC provides the applicant company with a right to a hearing before the Committee adopts its final opinion on an application. To date, the Committee has held four such hearings with pharmaceutical companies. In the light of experience, the Committee has issued new guidance for companies on the conduct of hearings (Annex 4).

It is important to note that hearings take place in a multi-lingual environment and that simultaneous technical interpretation during the hearing is necessary. Given the heavy workload of the Committee, the time available for hearings is limited. Therefore, a hearing cannot be used as an opportunity to resolve extensive technical points or to resolve deficiencies in the dossier. Rather, the hearing provides an opportunity for the applicant to present its point of view on basic questions concerning the evaluation of the benefits and risks presented by a particular product once all the technical aspects of the file have been clarified.

For this reason, the CVMP will not schedule the date for a hearing until replies have been received from the company to all outstanding questions, and the issues for discussion at the hearing have been fully clarified.

5. EVALUATION OF THE SAFETY OF RESIDUES

5.1 Introduction

The administration of veterinary medicinal products to food producing animals is likely to result in very small quantities of residues of the product or its metabolites being present in foodstuffs of animal origin. In order to ensure the proper protection of public health within the Community, it is therefore necessary to ensure that this residue is maintained at as low a level as is possible and is without risk for the consumer of foodstuffs of animal origin. Historically, the traditional approach to the regulation of residues was based on a concept of zero residue. However, this concept is a function of the sensitivity of the analytical methods used to detect residues, and in recent years considerable advances in analytical methodology have made it possible to detect residues at ever-lower levels.

For this reason, in February 1989, the Commission proposed that the Community should be empowered to adopt maximum residue limits (MRLs) for the individual compounds used in food producing animals after a scientific evaluation of the safety of the compound concerned to be undertaken by the CVMP.

On 26 June 1990, following a favourable opinion from the European Parliament, the Council adopted Regulation (EEC) 2377/90 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin. Once this regulation comes into effect, on 1 January 1992, Member States will not be able to authorize any new active substance for use in veterinary medicine unless a Maximum Residue Limit has been agreed by the Community. In addition, the Community must establish MRLs for all active compounds currently authorized for use in food producing animals over the five year period 1992-1996.

In order to prepare for the entry into force of the new regulation, the CVMP is currently preparing a "Notice to Applicants" explaining how to prepare and present applications for the establishment of MRLs and a timetable for the evaluation of existing compounds.

However, even before the adoption of the new regulation, the CVMP, had begun consideration of the general principles to be applied in the safety evaluation of residues, and had begun the evaluation of certain widely used priority compounds. In November 1990, the CVMP approved recommendations for MRLs for 21 compounds. These recommendations are set out in Annex 5 of this report, and copies of the summaries of the evaluations of these compounds undertaken by the CVMP are available in English or French upon request from the Pharmaceutical Unit of the Commission.

Written comments are invited from industry and other interested parties on these recommendations for MRLs. Any comment should be addressed in writing to the Secretariat of the CVMP, at the address given in Annex 2, to arrive before 1 September 1991. Subject to any further comments from Member States or other interested parties, it is the intention of the Commission to present these proposals for adoption in accordance with Council Regulation 2377/90 as soon as possible after 1 January 1992.

5.2 Current procedure for the evaluation of residues within the CVMP

Within the CVMP, the evaluation of the safety of residues is undertaken by the residues working party, which includes experts from all Member States. Any member of the working party may propose that a particular compound should be the subject of a review by the group. The group as a whole considers the list of compounds proposed and establishes a priority list.

The group then appoints one of its members to act as rapporteur for the compound, and to prepare a monograph on the available data. In order to avoid unnecessary duplication of effort, the rapporteur is usually selected from a Member State which has recently reviewed or is in the process of reviewing the compound concerned at national level.

The monograph, including proposals for MRLs, is then discussed by the whole group, and requests for clarification or amendment of the monograph may be put to the rapporteur. Once the group has reached a consensus on the evaluation of the compound, the rapporteur prepares a summary of the evaluation which is forwarded to the CVMP for approval and then published by the Commission.

The working methods of the group have developed informally, and are based on administrative cooperation between Member States. Any necessary liaison with the commercial sponsors of the compound is normally undertaken by the administration of the Member States, although occasionally a company may be invited to make a presentation before the group. However, once Regulation 2377/90 has entered into force, the work of the group will be put on a formal basis, and provision will be made for a formal hearing of the companies concerned.

5.3 The principles of the safety evaluation of residues

The approach used by the CVMP and its residues working party for the evaluation of the safety of residues is broadly similar to the approach used by other scientific bodies charged with the safety evaluation of food additives and contaminants. In particular, there are many similarities between the methods used by the CVMP and the WHO/FAO Joint Expert Committee on Food Additives which undertakes the evaluation of the safety of residues of veterinary drugs on behalf of the Codex Alimentarius. Indeed, several members of the CVMP residues working party have been invited in a personal capacity to serve on JECFA.

Nevertheless, there are certain specific differences between the evaluation of the safety of residues of veterinary medicines and the evaluation of other residues or food additives or contaminants. First, because of the properties of the active substances used in veterinary medicine, account must be taken not only of the toxicological properties of the compounds in the limited sense of the term (such as teratological, mutagenic or carcinogenic effects) but also of their pharmacological properties and their possible allergenic potential. Moreover, in the case of antibiotics and similar compounds, the possibility of a microbiological risk to the make-up of the human gut flora may also need to be considered. Secondly, the residue to which the consumer of foodstuffs of animal origin is exposed are not necessarily the same as the parent drug substance, since the product is metabolised within the treated animal.

Following the completion of the various pharmacological, toxicological and other tests undertaken to demonstrate the safety of the compound, the first major stage in the process of safety evaluation is the establishment of the acceptable daily intake (ADI). The ADI is an estimate of the residue, expressed in terms of micrograms or milligrams per kilogram of bodyweight, that can be ingested daily over a lifetime without appreciable health risk. It indicates a range from zero to an upper limit. The basis for the calculation of the ADI is the no-observed-effect level (NOEL) with respect to the most sensitive parameter in the most sensitive appropriate test species, or in some cases, in humans. A safety factor (SF) is then applied to provide a margin of safety, taking into account the inherent uncertainties in extrapolating animal toxicity data to human beings and to take account of variations within the human species. In selecting a safety factor, it is usually assumed that human beings are ten times more sensitive than the test animal, and that there is a ten-fold range of sensitivity within the human species. Thus, where good quality data are available, a safety factor of 100 is usually applied, although this may be increased or reduced depending on the nature and quality of the data available and of the effects observed in animals or man.

Where the available data are sufficient to demonstrate that exposure to residues over several years will not present a risk to health, but there are insufficient data to guarantee safety over a life-time, a temporary ADI may be accepted, using a higher safety factor.

The ADI concept is not applicable to substances for which it is not possible to determine a NOEL because they demonstrate non-threshold effects. In such cases, an alternative approach to safety evaluation applied on a case by case basis, having regard to all the data available.

Once the ADI has been agreed, it is then necessary to determine MRLs for the individual food commodities concerned. Since the ADI is related to body weight, an arbitrary average human bodyweight is defined at 60 kg. The ADI is therefore multiplied by 60 to give the total amount of residue which can be ingested by a human being.

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

Thus for the purpose of deriving MRLs from the ADI it is assumed that the average person consumes, on a daily basis, 500 g of meat (made up of 300 g of muscle, 100 g of liver, 50 g of kidney and 50 g of fat) together with 1.5 litres of milk and 100 g of eggs or egg products. The total amount of residues present in this daily food package is not allowed to exceed the ADI.

MRLs are then allocated to the individual food commodities concerned; muscle tissue, liver, kidney, fat, eggs and milk. At this stage, account is also taken of the pattern of residue depletion of the compound through the target animal, and the possible lengthy persistence of residues in specific organs such as the liver or kidneys, or at the injection site. The MRLs allocated to animal tissues usually apply to all species, unless otherwise stated.

Once the process of safety evaluation is complete, and MRLs have been derived for a particular compound, consideration is then given to the likely level of residue which may be expected to remain after the use of the compound in accordance with good veterinary practice, and to the availability of analytical detection methods suitable for use for routine monitoring purposes. The MRLs may be further reduced, but never increased, to take account of these factors.

Once MRLs have been allocated, it is then necessary to determine withdrawal periods during which the target animal must not be slaughtered, or during which milk or eggs must not be taken for human consumption, which ensure that residues from the product concerned will not exceed the MRLs. Since the duration of the withdrawal period will depend on the individual pharmaceutical formulation concerned, withdrawal periods are currently determined by Member States as part of the overall process of evaluation of the application for marketing authorization. The CVMP has recently agreed certain general principles to be taken into consideration for the determination of withdrawal periods (Annex 6), and consideration is being given to the preparation of more detailed guidelines.

6. INTERNATIONAL RELATIONS

Through the intermediary of the Commission, good relations have been established between the CVMP and the Nordic Council of Medicines. An observer from the Nordic Council attends meetings of the efficacy working party and a regular exchange of guidelines takes place.

Following the establishment of bilateral liaison meetings between the Commission and the United States Food and Drug Administration, a regular exchange of information takes place. The expertise of the CVMP has been essential for the preparation of the specific bilateral sessions devoted to veterinary medicines which take place at each meeting.

The expertise provided by the CVMP is also of great value in preparing coordinated Community positions for the annual meetings of the Codex Alimentarius Committee on Residues of Veterinary Drugs in Foods, and for other international contacts in this area.

7. PROGRAMME OF ACTIVITY FOR 1991

In conclusion to this report it appears appropriate to highlight some of the major priorities for the work of the Committee during 1991.

In addition to the continuing process of evaluation of applications for authorization submitted under the Community procedures, and continuation of the programme of preparation of guidelines, it appears that the major task of the Committee will be to prepare for the entry into force of the three new legislative measures which were adopted by the Council during 1990 and which have been mentioned at various points earlier in this report.

Other priority tasks will include the continuing implementation of the Committee's policy of transparency, the development of veterinary pharmacovigilance and the monitoring of the completion of the review of old veterinary medicines in October 1991.

LIST OF ANNEXES

1. Main Community legislative texts applicable to veterinary medicinal products.
2. Membership of the Committee
3. The Multi-State Procedure
4. Conduct of hearings before the CVMP
5. Maximum Residue Limits recommended by the CVMP
6. General principles for the establishment of withdrawal periods

ANNEX 1

Main Community legislative texts applicable to
veterinary medicinal products

Council Directive 81/851/EEC of 28 September 1981 on the approximation of laws of the Member States relating to veterinary medicinal products (O.J. N° L 317, 6.11.1981)

Council Directive 81/852/EEC of 28 September 1981 on the approximation of laws of the Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of veterinary medicinal products (O.J. N° L 317, 6.11.1981)

Council Directive 87/20/EEC of 22 December 1986 amending Directive 81/852/EEC of 28 September 1981 on the approximation of laws of the Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of veterinary medicinal products (O.J. N° L 15, 17.1.1987)

Council Directive 87/22/EEC of 22 December 1986 on the approximation of national measures relating to the placing on the market of high-technology medicinal products, particularly those derived from biotechnology (O.J. N° L 15, 17.1.1987)

Council Regulation (EEC) N° 2377/90 of 26 June 1990 laying down a Community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin
(O.J. N° L 224, 18.8.1990, p. 1)

Council Directive 90/676/EEC of 13 December 1990 amending Directive 81/851/EEC on the approximation of laws of the Member States relating to veterinary medicinal products.
(O.J. N° L 373, 31.12.1990, p. 15)

Council Directive 90/677/EEC of 13 December 1990 extending the scope of Directive 81/851/EEC on the approximation of laws of the Member States relating to veterinary medicinal products and laying down additional provisions for immunological veterinary medicinal products.
(O.J. N° L 373, 31.12.1990, p. 26)

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

APPLICATIONS UNDER DIRECTIVE 81/851/EEC

"THE MULTI-STATE PROCEDURE"

1. The firm consults the competent authority of the Member State which granted the initial authorization and agrees any changes which may be necessary to update the dossier.
2. The firm submits a complete application directly to the competent authorities of at least five Member States, indicating that the dossier is submitted in accordance with Article 17 of Directive 81/851/EEC, and that the Member State which granted the initial authorization has consented to the transmission of the documents directly by the applicant. The CVMP application form is annexed to the covering letter submitted with the application.

A copy of the dossier is also transmitted to the Secretariat.

3. Upon receipt of its copy of the dossier, the Secretariat notifies the Member States of the application by telex (Model Telex I) and invites the Member States directly concerned by the application to confirm receipt by telex or telefax.

If a Member State considers that the dossier is not acceptable for the purposes of assessment, it immediately informs the Secretariat, which invites the applicant to correct the application (Standard Form Letter 1).

4. Once all Member States have confirmed receipt of the dossier, the Secretariat sends a second telex announcing the start of the 120 period allowed for the submission of reasoned objections in accordance with Article 18(2) of Directive 81/851/EEC (Model Telex II).

Only one telex per month will be sent, announcing the start of the 120 day period for all multi-state applications that month.

An opinion of the CVMP is not required if no Member State has put forward any reasoned objection during the 120 day period.

5. A Member State sends any reasoned objections it may have directly to the applicant with copies to the Secretariat and to the Member State which granted the initial authorization, within the 120 day period. The Secretariat circulates all objections received to all Member States.

As soon as the first objection is received from a Member State, the Secretariat forwards that objection to the applicant together with Standard Form Letter 2. The Secretariat also forwards all objections subsequently received to the applicant. If the applicant chooses to submit further observations to the Committee, he is expected to include a consolidated list of questions from all Member States together with his responses.

6. In principle, the opinion of the Committee is given within a further 60 days. The opinion deals with whether, in the light of the objections put forward by Member States, the application may be accepted.

However, the applicant may submit further observations or particulars to the Committee in response to the objections of the Member States. The applicant should discuss the nature of this response with the competent authority of the Member State which granted the initial authorization, who will act as rapporteur for the Committee. A single submission should be prepared, covering all the objections put forward (questions and answers).

The format of the response is the same as the order of presentation of the dossier and the same rules as to language apply. However, depending on the Member States concerned by the application, it will be helpful if this response can be prepared in English and French.

This submission must be transmitted to the Secretariat and the members of the CVMP by name at least 30 days before the date of the meeting, in the format of the Notice to Applicants.

In order to allow time for the preparation of replies, the applicant may request the Committee to postpone the adoption by up to 90 days.

Any such request must first be agreed with the rapporteur. It should be submitted in writing to the Secretariat (telex or telefax may be used) and should contain a firm commitment from the company as to the date by which the additional information will be circulated to all Member States and the Secretariat.

7. Although Directive 81/851/EEC does not give any right to a hearing before the Committee, the CVMP has decided that it would be prepared to consider a request for a hearing where examination of the application has disclosed the existence of important questions of Community interest on which it would be useful to hear the point of view of the applicant. A decision on such a request, which should be submitted as soon as possible, shall be taken by the Chairman and the two vice-chairmen in consultation with the rapporteur.
8. At the CVMP meeting, the rapporteur reports on the extent to which the reasoned objections have been resolved. The hearing (if any) takes place. Following discussion, the Committee prepares a draft opinion, in consultation with the rapporteur. The Committee adopts the opinion on the second day.
9. As soon as possible after the meeting, the opinion of the Committee is transmitted to the Permanent Representations of the Member States. Within 30 days the Member States reach a decision on the application for marketing authorization, and inform the Committee thereof.

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

**Notes for guidance
on the conduct of hearings before the Committee**

In the light of the experience acquired, the Committee for Veterinary Medicinal Products has decided to issue further guidance to assist applicants in the preparation of oral hearings before the Committee. This guidance should be read together with the guidance given in Part II, Section 5 of the notice to applicants.

1. At least four weeks before the date on which the Committee proposes to consider the application;
 - the applicant must indicate in writing to the Secretariat whether or not he wishes to appear for a hearing before the Committee. Any request for audio-visual equipment must also be made at this time.
 - the applicant must circulate in writing to all Member States and the Commission any additional information which he wishes to be considered in connection with the hearing. A covering letter should clearly indicate the name of the product concerned, should summarise the additional information submitted and its relationship with the outstanding questions of the Committee and should indicate that it is for use in connection with the CVMP hearing. In the event that this information is voluminous, the applicant should consider requesting a postponement of the hearing, to enable proper consideration of the information. The Committee also reserves the right to disregard such information or to require a postponement of the hearing if insufficient time is allowed for the consideration of the information.
2. At least one week before the hearing the applicant provides the Secretariat with a definitive list of the names and addresses of the representatives of the company for the hearing. For security reasons, proof of identity must be provided to gain access to Commission buildings.

3. **Before the start of the hearing** : applicants are advised to arrive 30 minutes before the scheduled start of their hearing. They should bring with them 35 hard copies of any visual materials for use by the interpreters and members of the Committee. Each page of such materials must be clearly numbered to permit rapid identification of copies of individual slides, in particular by the interpreters. Care should be taken to ensure that visual materials are legible at a distance of 25 metres.
4. **Conduct of the hearing** : hearings will usually be conducted in the following sequence:
 - the Chairman will invite the representatives of the applicant to introduce themselves;
 - the applicant will be invited to make a brief general presentation of the product, which should not exceed 10 minutes. At this stage the applicant should not go into detail on the answers to the outstanding questions of the Committee.
 - the chairman will then invite the rapporteur to put the outstanding questions of the Committee, one at a time, usually in the order quality, safety, efficacy. After each answer from the company, an opportunity will be given to the other Member States to ask supplementary questions before moving on to the next question.
 - at the end of the hearing, the applicant will be asked to withdraw while the Committee considers its opinion which will be sent in writing to the company.
5. **References to specific studies** : when referring to specific studies or test results, the representatives of the company should state clearly whether these were contained in the original submission, in the initial replies of the company to the questions put by the Committee or in a further submission which may have been made in preparation for the hearing.
6. **Introduction of new information during the hearing** : the Committee wishes to discourage companies in the strongest possible terms from providing new information only at the hearing. Where such information is provided, the Committee reserves the right either to disregard it for the purpose of the opinion, or to postpone the opinion to allow time for the consideration of the new information.

ANNEX 5

MAXIMUM RESIDUE LIMITS RECOMMENDED BY
THE COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS
FOR RESIDUES OF CERTAIN ACTIVE SUBSTANCES
USED IN VETERINARY MEDICINE

This Annex contains 21 recommendations for MRLs for certain active substances used in veterinary medicines.

Copies of summaries of the evaluation of these compounds by the Committee for Veterinary Medicinal Products are available upon request, in English or in French, from the Secretariat of the Committee within the Commission of the European Communities at the address given in Annex 2.

Comments on these recommendations are invited from interested parties, and should reach the Commission before 1 September 1991.

TABLE OF MAXIMUM RESIDUE LIMITS RECOMMENDED BY THE COMMITTEE FOR VETERINARY
MEDICINAL PRODUCTS FOR RESIDUES OF CERTAIN ACTIVE SUBSTANCES
USED IN VETERINARY MEDICINE

Notes for reading the table

1. ADI stands for Acceptable Daily Intake. It is presented in a range from 0 up to the maximum acceptable daily intake expressed in terms of micrograms per kilogram of bodyweight per day. The entry N/A under the ADI column means that no ADI has been allocated for the compound concerned.
2. MRL stands for Maximum Residue Limit. The MRL is expressed in terms of a marker residue, which may be the parent drug, a metabolite, or a combination thereof. Unless otherwise stated, the marker residue is the same for all target food commodities. For example, in the case of febantel (No 8), the marker residue is the sum of oxfendazole, oxfendazole sulfone and fenbendazole found in the target food commodity.
3. The target food commodity represents the food commodities in which the residue may be expected to be present.

The reference "meat, all tissues" means muscle, kidney, liver and fat.

Unless otherwise stated, MRLs for meat tissues cover all species including bovine, ovine, porcine, equine, poultry and aquatic species.

Where compounds are authorized for use in laying birds or lactating animals, eggs or milk, as appropriate, are always included among the target food commodities. If eggs or milk are not included it means that the compound concerned is not authorized for use in laying birds or lactating animals, and no residues should be present in these food commodities.

4. The last column indicated the status of the MRL.

If the term "final" is used, this means that the CVMP considers that sufficient data is available to enable a definitive MRL to be adopted, and to enable the compounds concerned to be included in Annex I of Council Regulation 2377/90.

"Prov" means provisional. If this term is used, it means that the Committee considers that the data available is not sufficient to determine a definitive MRL. However, sufficient data is available to permit the establishment of a provisional MRL, and to enable the compound to be included in Annex III of Council Regulation 2377/90. The date following the reference to provisional is the time limit recommended by the Committee for the submission of the additional data necessary to enable a final MRL to be established.

TABLE OF MAXIMUM RESIDUE LIMITS RECOMMENDED BY THE COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS
FOR RESIDUES OF CERTAIN ACTIVE SUBSTANCES USED IN VETERINARY MEDICINE

<u>COMPOUND</u>	<u>ADI</u>	<u>MRL(s)</u>	<u>MARKER RESIDUE</u>	<u>TARGET FOOD COMMODITY</u>	<u>STATUS</u>
1. Chloramphenicol	N/A	10 µg/kg	Parent drug	Meat, all tissues*	Prov, 1.1.94
2. Sulfonamides group	N/A	100 µg/kg 100 µg/kg	Parent drug	Meat, all tissues, Milk	Final Prov, 1.1.94
3. Trimethoprim	N/A	50 µg/kg	Parent drug	Meat, all tissues, milk	Final
4. Nitrofurans group	N/A	5 µg/kg	All residues with intact 5-nitro structure	Meat, all tissues, eggs	Prov, 1.1.93
5. Dapsone	0-3.5 µg/kg bw/d	25 µg/kg	Parent drug	Meat, all tissues, milk	Prov, 1.1.94
6. Dimetridazole	N/A	10 µg/kg	All residues with intact nitro-imidazole structure	Meat, all tissues	Prov, 1.1.94
7. Ronidazole	N/A	2 µg/kg	All residues with intact nitro-imidazole structure	Meat, all tissues	Prov, 1.1.94

* No MRLs are allocated for residues of chloramphenicol in milk or eggs because the CVMP specifically recommends that this compound not be authorised for use in lactating animals or laying birds.

<u>COMPOUND</u>	<u>ADI</u>	<u>MRL(s)</u>	<u>MARKER RESIDUE</u>	<u>TARGET FOOD COMMODITY</u>	<u>STATUS</u>
8. Febantel*	N/A	1000 µg/kg 10 µg/kg 10 µg/kg	oxfendazole + oxfendazole - sulphone + fenbendazole	Liver Muscle, kidney, fat Milk	Prov, 1.1.92 Prov, 1.1.92 Prov, 1.1.92
9. Fenbendazole*	N/A	1000 µg/kg 10 µg/kg 10 µg/kg	oxfendazole + oxfendazole - sulphone + fenbendazole	Liver Muscle, kidney, fat Milk	Prov, 1.1.92 Prov, 1.1.92 Prov, 1.1.92
10. Oxfendazole	0-2.5 µg/kg bw/d	1000 µg/kg 10 µg/kg 10 µg/kg	oxfendazole + oxfendazole - sulphone	Liver Muscle, kidney, fat Milk	Prov, 1.1.92 Prov, 1.1.92 Prov, 1.1.92
11. Ivermectin	0-0.2 µg/kg bw/d	15 µg/kg 20 µg/kg	H2B1a metabolite	Liver Fat	Final Final
12. Levamisol	N/A	10 µg/kg	Parent drug	Meat, all tissues, milk	Prov, 1.1.95
13. Carazolol	0-0.2 µg/kg bw/d	50 µg/kg 5 µg/kg	Parent drug	Liver, kidney Muscle, fat	Prov, 1.1.92 Prov, 1.1.92
14. Azaperone	0-0.8 µg/kg bw/d	100 µg/kg 50 µg/kg	Azaperol Azaperol	Kidney Liver, muscle, fat	Prov, 1.1.92 Prov, 1.1.92

* The Committee was agreed that there is no need to establish separate ADIs for febantel and fenbendazole because these are metabolised into oxfendazole, which is the more toxic metabolite.

<u>COMPOUND</u>	<u>ADI</u>	<u>MRL(s)</u>	<u>MARKER RESIDUE</u>	<u>TARGET FOOD COMMODITY</u>	<u>STATUS</u>
15. Benzylpenicillin	N/A	50 µg/kg 4 µg/kg	Parent drug	Meat, all tissues Milk	Final Final
16. Ampicillin	N/A	50 µg/kg 4 µg/kg	Parent drug	Meat, all tissues Milk	Final Final
17. Amoxicillin	N/A	50 µg/kg 4 µg/kg	Parent drug	Meat, all tissues Milk	Final Final
18. Oxacillin	N/A	300 µg/kg 30 µg/kg	Parent drug	Meat, all tissues Milk	Final Final
19. Cloxacillin	N/A	300 µg/kg 30 µg/kg	Parent drug	Meat, all tissues Milk	Final Final
20. Dicloxacillin	N/A	300µg/kg 30µg/kg	Parent drug	Meat, all tissues Milk	Final Final
21. Tetracyclines group	0-3 µg/kg bw/d	600 µg/kg 300 µg/kg 200 µg/kg 100 µg/kg 100 µg/kg 10 µg/kg	Parent drug	Kidney Liver Eggs Muscle Milk Fat	Prov, 1.1.94 Prov, 1.1.94 Prov, 1.1.94 Prov, 1.1.94 Prov, 1.1.94 Prov, 1.1.94

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

General considerations for the establishment of
withdrawal periods for veterinary medicinal products

The protection of consumers of foodstuffs of animal origin against possible harmful effects resulting from the ingestion of residues of veterinary medicinal products depends upon three factors:

1. the safety assessment of residues of pharmacologically active compounds used in veterinary medicine, leading, where necessary, to the determination of an acceptable daily intake without risk for the consumer, and maximum residue limits (MRLs) for edible food commodities;
2. the determination of the withdrawal period necessary to ensure that foodstuffs taken from treated animals do not contain residues in excess of the MRLs;
3. the routine control of foodstuffs of animal origin, to ensure that the MRL is not in practice exceeded.

The withdrawal period is the interval necessary between the last administration to animals of the veterinary medicinal product under normal conditions of use and the time when treated animals can be slaughtered for the production of foodstuffs, or the time during which milk and eggs must be discarded due to the likely presence of unsafe residues of the medicinal product in these foodstuffs.

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

If the withdrawal period is to fulfill its purpose as a practical instrument for the protection of public health, it is important to ensure that the withdrawal period can in practice be observed. This implies that the length of the withdrawal period must be compatible with the normal conditions of use of the veterinary medicinal product.

The preamble to Directive 81/852/EEC sets out the fundamental principle that a decision to authorize a veterinary medicinal product can only be taken after an evaluation of the quality, safety and efficacy of the medicinal product concerned. The applicant is required to demonstrate that the potential hazards of a veterinary medicinal product are outweighed by the therapeutic efficacy of the product. Failing such a demonstration, the application must be rejected.

Both the duration of the withdrawal period and the practical feasibility of observance of the withdrawal period are therefore aspects of the potential hazard which need to be taken into consideration when deciding whether or not authorization may be granted.

In general terms, it is likely that problems of observance of withdrawal periods will be greatest in the case of veterinary medicinal products intended for use in animals producing foodstuffs on a daily basis such as eggs or milk. Particular problems arise in the case of products intended for the mass medication of laying birds in large-scale production units, where any withdrawal period may be unacceptable.

The Committee for Veterinary Medicinal Products has been informed that in the case of older veterinary medicinal products, which have been on the market for many years, the information available about residue kinetics is often insufficient. As a result, the competent national authorities take a conservative approach to the determination of withdrawal periods and sometimes use an additional safety span when determining withdrawal periods for these products. The problem which then arises is whether such lengthy withdrawal periods are compatible with the normal conditions of use of these products.

In order to support the maintenance on the market of these old products, the Committee would encourage manufacturers to conduct residue depletion studies, so that the information necessary for the establishment of adequate but realistic withdrawal periods may be provided.