EUROPEAN COMMISSION
DIRECTORATE-GENERAL III
INDUSTRY
Industrial affairs III: Consumer goods industries
Pharmaceuticals

III/5056/95

Draft

NOTICE TO APPLICANTS FOR MARKETING AUTHORISATION FOR VETERINARY MEDICINAL PRODUCTS IN THE EUROPEAN UNION

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NOTICE TO APPLICANTS

FOREWORD

This Notice to Applicants has been prepared by the European Commisson, in consultation with the competent authorities of the Member States (Committee for Veterinary Medicinal Products and its Operations Working Party).

This Notice has no legal force and does not necessarily represent the final views of the Commission. In case of doubt, therefore, reference should be made to the appropriate Community Regulations and Directives. It is important, when reading this text, to appreciate that the legal requirements of the Directives and the Regulation must be met and that this Notice presents the preliminary views of the Member States on how those requirements may be met.

This current draft is being issued for a period of consultation and comments are therefore invited by 1 June 1995. During this period, further improvements to the text may be possible due to:

a) the establishment of the new Committee for Veterinary Medicinal Products, within the European Agency for the Evaluation of Medicinal Products, and its experience with the new procedures;

b) some practical experience in the Member States with the operation of the mutual recognition procedures;

c) experience of companies in operating these procedures.

The requirements for the content of the application dossier are set out in Directive 81/852/EEC as amended. The 1993 edition of Volume VB presents the structure and content of the dossier for application for marketing authorisation and Volume VI does so for applications for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin. This guidance remains currently valid.

CHAPTER I

GENERAL INTRODUCTION

1. OBJECTIVES

The primary purpose of any rules governing medicinal products is to safeguard the public health. However, this objective must be achieved by means which do not hinder the development of the pharmaceutical industry or trade in medicinal products within the Community. Thus, the pharmaceutical legislation of the European Community has consistently pursued the twin objectives: the protection of public health and the free movement of medicinal products.

2. MARKETING AUTHORISATION

A veterinary medicinal product may only be placed on the market of a Member State if a marketing authorisation has been issued by the competent authority of that Member State (national authorisation) or an authorisation has been granted in accordance with Regulation (EEC No. 2309/93 (Community authorisation)).

For veterinary medicinal products intended for food-producing animals containing a pharmacologically active substance not already authorised in the Member State for the concerned species, the safety of residues must have been evaluated in accordance with Regulation (EEC) Nr. 2377/90, taking into account Volume VI of the Rules governing Medicinal Products in the European Union.

For applications made after the 1.1.1995, the person responsible for placing the medicinal product on the market must be established within the Community. For medicinal products already on the market, this requirement will be applied at the time of the 5 year renewal.

2.1 National authorisations

The competent authorities of the Member States are responsible for the granting of marketing authorisations for medicinal products which are placed on the market in that Member State. Important exceptions to this provision occur :

- medicinal products developed by means of one of the biotechnological processes referred to in Regulation (EEC) No. 2309/93, Annex, Part A, which may only be authorised by the Community;
- veterinary medicinal products, including those not derived from biotechnology, intended primarily for use as performance enhancers in order to promote the growth of treated animals or to increase yields from treated animals (Regulation (EEC) No. 2309/93, Annex, Part A);
- medicinal products referred to in Regulation (EEC) No. 2309/93, Annex, Part B, which may, at the request of the person responsible for placing it on the market, be authorised by the Community.

In order to obtain a national marketing authorisation, an application must be submitted to the competent authority of the Member State. In cases where national authorisations are

requested in more than one Member State, an application must be submitted in each Member State (see Chapter VII for number of dossiers and languages accepted). For national applications, whether part of a mutual recognition procedure or not, the language requirements of the Member State always apply.

For marketing authorisations in more than one Member State, the person responsible for placing the product on the market may

- make an application in one of the Member States and once the marketing authorisation has been granted, make applications in other Member States concerned, requesting them to mutually recognise the marketing authorisation already granted (see Chapter II for further details).
- make (parallel) applications in each of the Member States concerned and request a national authorisation in each (after 1.1.1998, Member States are required to mutually recognise the first marketing authorization decision).

2.2 Mutual recognition

Mutual recognition procedures may arise in four instances:

i) in accordance with Article 17.1 of Directive 81/851/EEC as amended: where 'in order to obtain the recognition according to the procedures laid down in this Chapter in one or more of the Member States of an authorization issued by a Member State in accordance with Article 4 (of Directive 81/851/EEC), the holder of the authorization shall submit an application to the competent authorities of the Member State or Member States concerned';

ii) in accordance with Article 8.2 of Directive 81/851/EEC as amended: 'where a Member State notes that an application for authorization submitted after 1 January 1995 is already under active examination in another Member State in respect of that veterinary medicinal product, the Member State concerned may decide to suspend the detailed examination of the application on order to await the assessment report prepared by the other Member State in accordance with Article 5b'.

iii) in accordance with Article 19 of Directive 81/851/EEC as amended 'if several applications submitted in accordance with Article 5 and 5a of Directive 81/851/EEC have been made for marketing authorization for a particular veterinary medicinal product, and Member States have adopted divergent decisions concerning the authorization of that veterinary medicinal product, or its suspension or withdrawal from the market, a Member State, or the Commission, or the person responsible for placing the aforementioned product on the market may refer the matter to the Committee for application of the procedure laid down in Article 21 (of Directive 81/851/EEC)';

iv) in accordance with Article 20 of Directive 81/851/EEC as amended: 'the Member States or the Commission or the applicant or the holder of the marketing authorization may, in specific cases where the interests of the Community are involved, refer the matter to the Committee for the application of the procedure laid down in Article 21'.

2.3 Community authorisations

The Community is responsible for the granting of marketing authorisations for medicinal products

- developed by means of one of the biotechnological processes referred to in Regulation (EEC) No. 2309/93, Annex, Part A, which may only be authorised by the Community;
- veterinary medicinal products, including those not derived from biotechnology, intended primarily for use as performance enhancers in order to promote the growth of treated animals or to increase yields from treated animals (Regulation (EEC) No. 2309/93, Annex, Part A);
- medicinal products referred to in Regulation (EEC) No. 2309/93, Annex, Part B, which may, at the request of the person responsible for placing it on the market, be authorised by the Community.

In order to obtain a Community authorisation, an application must be submitted to the European Agency for the Evaluation of Medicinal Products (EMEA) (see Chapter VII for number of dossiers required).

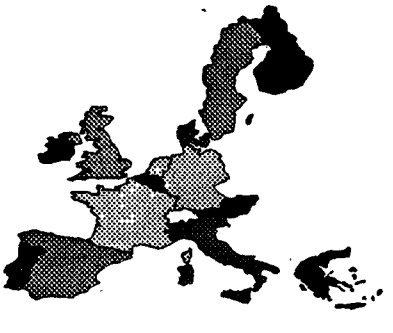
The scientific evaluation of the application is carried out within the scientific committees of the Agency, and a scientific opinion is prepared. The opinion is sent to the European Commission which drafts a decision. Having consulted with the relevant Standing Committee, normally the Commission adopts the Decision and grants a marketing authorisation[1] (see Chapter IV for further details).

3. ACCESS TO THE MARKET

The free movement of medicinal products within the Community has been greatly enhanced by the adoption of the new system of marketing authorisation.

Thus access to the Community market may be achieved in a number of ways :

- 15 applications in 15 Member States (with the benefit of mutual recognition: 15/15 = 1 single market)
- a single application using the centralised procedure = 1 single market



15/15 = 1 single market

1 single market

[1] In cases where there is not a qualified majority in favour of the draft Commission Decision, the matter is referred to Council.

The operational aspects of the mutual recognition procedures are given in Chapters II and III, whilst for the centralised procedure, this is set out in Chapter IV.

In the legislative texts for the new systems of marketing authorization, there are a range of options for a regulatory strategy. Thus, a company may choose to use a mutual recognition route or a centralised route to access the single market (within the framework set out by the texts) or continue to submit parallel national applications (after 1.1.1998, Member States are required to mutually recognise the first marketing authorisation decision).

From an administrative point of view, however, a consistent regulatory strategy is important both for the applicant and for the competent authority. For example, using the mutual recognition procedure with Member State X as reference (originating) Member State for an application for a marketing authorization, followed by Member State Y for an abridged application (e.g. extension), and perhaps Member State Z for an other abridged application (e.g. a new indication), may not be the most efficient procedure and may pose problems for the management of the marketing authorization.

Therefore, it would be appropriate that the reference Member State for the first marketing authorization be used as the reference Member State for subsequent abridged applications for that medicinal product. The reference Member State for variations is, of course, the Member State which prepared the assessment report upon which mutual recognition was based or the Member State chosen in this respect by the marketing authorisation holder.

Equally for applications using Part B of the Annex of Regulation (EEC) No. 2309/93, the optionality provided for in the legislation should not be interpreted as a mechanism to partition the market. Thus for abridged applications (e.g. informed consent and extensions) the option to use either the centralised route or mutual recognition route is available. Where such abridged applications use the mutual recognition procedure, both the Member States and the Commission must take up their responsibilities regarding the maintenance of a harmonised market, including as necessary, availing of references in accordance with Article 20 of Directive 81/851/EEC as amended in cases of Community interest.

4. TRANSITION ARRANGEMENTS FOR COMMUNITY PROCEDURES

4.1 Fate of pending multi-state applications

A multi-state procedure was triggered when, in accordance with Article 17.1 of Directive 81/851/EEC as amended and in order to make it easier to obtain a marketing authorization in at least two Member States taking into due consideration an authorization issued in one Member State in accordance with Article 4 of Directive 81/851/EE, the holder of an authorization submits an application to the competent authorities of the Member States concerned together with the information and documents referred to in Articles 5, 5a and 5b of Directive 81/851/EEC.

Submissions made before the 31.12.94 (i.e. those for which the telex starting the 120 day period had been sent by the Commission before that date), which invoked Article 17.1 of Directive 81/851/EEC are considered as multi-state applications. On 1 January 1995, an inventory of such submissions was compiled.

For procedures which have not been completed, these remain for the new Committee to complete. These procedures will be completed in accordance with Directive 81/851/EEC

i.e. an opinion (where necessary) in accordance with Article 22 of Directive 81/851/EEC which is not legally binding and upon which Member States notify action taken within 60 days.

Neither these applications nor their variations fall within the scope of the mutual recognition procedures unless a new application or a referral (Articles 19, 20 or 42h of Directive 81/851/EEC as amended) is made.

4.2 Conversion of concertation to centralised procedure

Article 2 of Directive 93/41/EEC provides that *applications for marketing authorization which have been referred to the Committee for Proprietary Medicinal Products before 1 January 1995 in accordance with Article 2 of Directive 87/22/EEC and in respect of which the Committee has not given an opinion by 1 January 1995 shall be considered in accordance with Regulation (EEC) No 2309/93.*

In these cases the legislative texts provide for the conversion of former concertation procedures, for which an opinion had not been adopted by 1 January 1995, into centralised applications. In order to ensure a smooth transition, a number of practical issues were considered. A series of pragmatic options were developed

i) timetable: the time scale for the opinion in both the concertation and centralised procedure is 210 days (120 plus 90 in exceptional cases for the concertation procedure). The date of receipt of a valid application starts this period.

Normally, the Committee adopted the timetable proposed by the rapporteur for the review of the application at a CVMP meeting. In order to adopt the timetable, submissions must have been made (and validated) in the concerned Member States before the meeting in question. Applications not validated and accepted within the concertation procedure will therefore have to be treated in accordance with Regulation (EEC) No 2309/93.

ii) rapporteur: in the concertation procedure, the applicant will have selected the Member State acting as rapporteur and a co-rapporteur may have been identified. Depending on the stage of advancement of the procedure, that rapporteur will have prepared an assessment report and may even have prepared a draft opinion on behalf of the Committee.

In order to ensure a smooth transition from the concertation procedure to the centralised procedure, it is the intention that the future Committee would confirm that the rapporteurship would be continued by a member of the Committee belonging to the competent authority of the Member State which was previously rapporteur.

iii) assessment: as the composition and mandate of the committee changed (1.1.95), and in order to retain the assessment work of the previous rapporteurs, the rapporteur's assessment report, consolidated list of questions, assessment of responses etc. which had already been prepared would be taken up by the new Committee. In order to facilitate this pragmatic approach, the working methodology of the Committees during 1994 moved towards that of the future system (e.g. appointment of a co-rapporteur, preparation of a committee assessment report, labelling, package insert, etc.).

4.3 Conversion of concertation to mutual recognition procedure

In the case of applications made in accordance with List A or B of Directive 87/22/EEC, for which the committee has already issued before 1 January 1995 an opinion, Member States will have already granted (or be in the process of granting) a national authorisation.

However, these applications have benefited from a Community procedure and a mechanism to maintain the harmonisation achieved has been foreseen in Article 23b of Directive 81/851/EEC as amended:

> *'Articles 23 and 23a shall apply by analogy to veterinary medicinal products authorised by Member States following an opinion of the Committee given in accordance with Article 4 of Directive 87/22/EEC before 1 January 1995'.*

Article 23 of Directive 81/851/EEC as amended provides for arrangements (for mutual recognition) of variations to such marketing authorizations by the person responsible for placing the veterinary medicinal products on the market. For these veterinary medicinal products which had been the subject of an opinion in the concertation procedure, the summary of product characteristics (SPC) was generally adopted. In cases where the SPC was not harmonised, it is important for marketing authorization holders to appreciate that any disharmony in the SPC could be a basis for arbitration when a request for a variation is submitted as the arbitration procedure of Article 21 and decision-making mechanism of Article 22 of Directive 81/851/EEC as amended applies to these veterinary medicinal products.

Article 23a of Directive 81/851/EEC as amended sets out the procedure for situations where a Member State considers that, for one of these medicinal products, a variation of the terms of a marketing authorization, its suspension or withdrawal is necessary for the protection of animal or public health or the environment.

The arrangements for variations to such products have been set out in Commission Regulation XX/95 (see Chapter II for details).

4.4 New applications for List A products

A question has arisen regarding medicinal products within the scope of List A of Directive 87/22/EEC. Some of the concertation procedures for List A products have included all Member States (existing before 1.1.95); for the others, as well as for those products which may not have been authorised in the new Member States before 1.1.95, the company may wish to make an application in previously unconcerned Member States.

Similarly, companies may wish to make abridged applications (Article 5.10 a, i or ii or iii) for these veterinary medicinal products, and/or wish to make new applications for extensions for these products.

Given that the Annex in Part A of Regulation (EEC) No 2309/93 is the same (or larger) in scope as the Annex List A of Directive 87/22/EEC, the question has arisen as to whether such new applications must use the centralised procedure. Following discussions with the Member States, a pragmatic approach has been considered, in order to avoid disruption in the marketplace.

Since such abridged applications make reference to the full dossier (already submitted in the Member States), the appropriate procedure could be the national one, co-ordinated through the principle of mutual recognition. Likewise, for new applications (either in Member States not previously concerned, or in new Member States) these could be treated as national applications co-ordinated through mutual recognition which would maintain the objective of a harmonised market.

For the purposes of mutual recognition, the Member State which acted as rapporteur for the concertation procedure would be the reference Member State for these applications.

5. APPLICATION FOR A MARKETING AUTHORIZATION

The legal basis for making an application for marketing authorisation is set out in Directive 81/851/EEC as amended.

The legal basis used for an application may be cumulative (i.e. Article 5.10 i) and iii)). In such cases the legal basis is a 'hybrid'. Further, the application dossier may be supplemented with additional tests and trials.

A brief description of the legal bases for making a marketing application is set out below. It is important, however, that the legal basis is not confused with the content of the application dossier, which is given in sections 8 to 10 of this Chapter.

5.1. Full applications

An application for marketing authorization must be accompanied by the particulars and documents set out in Article 5 of Directive 81/851/EEC. In cases where the exemptions in Article 5.10 (a) do not apply and therefore the results of

- physico-chemical, biological or microbiological tests,
- pharmacological and toxicological tests,
- clinical trials

are included in the dossier, the application is referred to as a 'full' application.

5.2. Abridged applications

The requirements which must be fulfilled in order to receive a marketing authorization are set out in Article 5 of Directive 81/851/EEC and include the provision of results of physico-chemical, biological or microbiological tests, pharmacological and toxicological tests and clinical trials. However, in the following situations, the results of pharmacological and toxicological tests or clinical trials do not have to be provided, thus allowing for an abridged application to be made.

Applications may be abridged in the following cases:

a) with an application for an essentially similar[2] veterinary medicinal product for which consent has been given by a marketing authorization holder to refer to its dossier (so called 'informed consent');

b) where the constituent or constituents of the veterinary medicinal product have a well established medicinal use, with recognised efficacy and an acceptable level of safety, demonstrated by detailed references to published literature presented in accordance with second paragraph of Article 1 of Directive 81/852/EEC (so called 'bibliographical');

c) a veterinary medicinal product which is essentially similar to a veterinary medicinal product which has been authorised in the Community for 6 years (may be extended to 10 years by a single decision of a Member State for all the products marketed on its territory) and is marketed in the Member State concerned; or 10 years for a veterinary medicinal product authorised by the Community in accordance with the provisions of Regulation (EEC) No. 2309/93.

5.2.1. Informed Consent from the marketing authorization holder

In accordance with Article 5.10 i) of Directive 81/851/EEC, the applicant is not required to provide the results of pharmacological and toxicological tests or clinical trials when the medicinal product is essentially similar and the marketing authorization holder has consented to the pharmacological, toxicological or clinical references contained in the dossier of the original product being used for the purpose of examining the application.

5.2.2 Bibliographical applications

During the period of exclusivity (6 or 10 years), an applicant wishing to use Article 5.10 (a)(ii) of Directive 81/851/EEC must fully satisfy all the requirements of Directive 81/851/EEC as amended.

Directive 81/852/EEC Article 1 states that "where pursuant to point 10(a) or (b) of the 3rd paragraph of Article 5 of Directive 81/851/EEC, references to published data are submitted, the provisions of this Directive [i.e. Directive 81/852/EEC] shall apply in like manner."

In such cases, the full article or reference should be supplied, with necessary translations. Moreover, the Expert Reports must clearly state the grounds for using published references under the conditions set out in Directive 81/852/EEC. This would include the completion of all of the tabular formats provided in the Notice to Applicants, where relevant. The impurity/related substances profile and the decomposition products arising during storage must be clearly indicated in order to allow assessment of appropriate efficacy and safety.

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2 The definition of "essentially similar" is taken to be:
"the same qualitative and quantitative composition in terms of active principles, *and*
the pharmaceutical form is the same, *and*
where necessary, appropriate bioavailability studies have been carried out"

In the event that detailed reference to published literature is not available to cover all the requirements, the applicant may supplement the missing data with appropriate additional studies.

5.2.3. Product essentially similar to a product authorised for 6 or 10 years

Essentially similar veterinary medicinal products are multi-source products interchangeable with a medicinal product which has been authorised in the Community for 6/10 years, and is marketed in the Member State concerned.

When a second applicant submits a dossier for a veterinary medicinal product which is essentially similar to a product which has been authorised for 6/10 years, bioequivalence should be substantiated (the need for appropriate bioavailability studies should be addressed in the dossier and Expert Report, cf. guideline on bioavailability and bioequivalence in Volume VII). The impurity/related substances profile and the decomposition products arising during storage must be clearly indicated in order to allow assessment of appropriate efficacy and safety. The excipients used should be justified by the manufacturer, well known, safe and suitable for the dosage form and compatible with the same efficacy and safety.

Under Directive 81/851/EEC as amended by Directive 87/20/EEC, the period of exclusivity, from the date of authorization in any of the Member States in the Community on the basis of a full dossier, is as follows:

- 10 years for veterinary medicinal products submitted through the centralised procedure of Regulation (EEC) No. 2309/93
- 10 years for veterinary medicinal products which have been authorised following an opinion of the CPMP in accordance with Article 4 of Directive 87/22/EEC (concertation procedure)
- 10 years (by single decision) for other veterinary medicinal products in Austria, Belgium, Germany, France, Italy, the Netherlands, Sweden and United Kingdom
- 6 years in Ireland and Luxembourg
- 6 years in Denmark, Finland, Greece, Spain and Portugal; however this period will not be applied beyond the date of expiry of a patent protecting the original product.

Evidence of the date of authorization for more than 6/10 years and the confirmation that the veterinary medicinal product is marketed in the Member States concerned should be provided in the application for marketing authorization. It should be noted that these periods do not prejudice the patent rights of the manufacturer of the original product. Any application for a marketing authorization submitted before the expiry of the periods referred to must be a full application.

After 6 or 10 years' knowledge and experience with a veterinary medicinal product, it would be inappropriate for ethical and scientific reasons to require a second applicant to repeat all tests, studies and trials, which are already known to the authorities. Appropriate data on the quality of the active substance and the dosage form must always be provided (in Part II of the dossier). However some guidance on the appropriate additional studies required is indicated in the following illustrative examples:

Abridged applications	*Additional data usually required*
Different salt/ester/complex/derivative (with the same therapeutic moiety) (after CVMP has confirmed that new MRLs are not required).	Evidence that there is no change in pharmacokinetics of the moiety, pharmacodynamics and/or in toxicity which could change the safety/efficacy profile. Otherwise to be considered as a new chemical entity
Different therapeutic use, in same target species, with same dosing regime	Part IV, Chapter II, clinical data
Therapeutic use in new species	Full Part IV + residue depletion studies
Different route/form of administration; - new route of administration - new oral form for immediate release - new dosage form for modified release	 Full Part IV + residue depletion studies Bioavailability Bioavailability + residue depletion studies + target animal tolerance studies, if necessary may suffice
Modification of dosing schedule and/or strength of unit doses	Bioavailability + residue depletion studies may suffice.

An abridged application for fixed combination products of known constituents may be appropriate where the constituents are known for 6/10 years and the requirements of the guideline on Fixed Combinations in Volume VII are met.

By extension, the concept of essentially similar also applies to different oral forms (e.g. tablets and capsules) with the same active substances for immediate release.

5.3 Extensions by existing marketing authorisation holders (so called 'extensions')

Extensions can only be used by the existing marketing authorisation holder.

Certain changes to a marketing authorization have to be considered to fundamentally alter the terms of this authorization and therefore cannot be considered as a variation. For these changes, set out in annex 2 of the regulations on variations and listed below, an application for a new marketing authorization must be made.

Appropriate data on the quality of the active ingredient and the dosage form must always be provided (in Part II of the dossier). In addition, necessary support of the safety and efficacy of the medicinal product must also be submitted.

1. Changes to the active substance(s):
i) addition of one or more active substance(s) including antigenic components for vaccines;
ii) deletion of one or more active substance(s) including antigenic components for vaccines;
iii) quantitative changes in the active substance(s);
iv) replacement of the active substance(s) by a different salt/ester complex/derivative (with the same therapeutic moiety),
v) replacement by a different isomer, a different mixture of isomers, of a mixture by an isolated isomer (e.g. racemate by a single enantiomer);
vi) replacement of a biological substance or product of biotechnology with one of a different molecular structure, modification of the vector used to produce the antigen/source material, including a master cell bank from a different source.
vii) a new ligand or coupling mechanism for a radiopharmaceutical

2. Changes to the therapeutic indications[3]
i) addition of an indication in a different therapeutic area, either treatment, diagnosis or prophylaxis
ii) change of the indication to a different therapeutic area, either treatment, diagnosis or prophylaxis;

3. Changes to strength, pharmaceutical form and route of administration
i) change of bioavailability
ii) change of pharmacokinetics e.g. change in the rate of release
iii) addition of a new strength
iii) change or addition of a new pharmaceutical form
iv) addition of a new route of administration

4. Other changes specific to veterinary medicinal products to be administered to food producing animals

i) addition or change of target species
ii)shortening of the withdrawal period

A marketing authorization as a result of a new application in accordance with annex 2 of the Regulations on variations, may be assimilated to an existing authorization (including where relevant, the existing authorization number) in accordance with the procedures operated by the competent authority.

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3 For parenteral administration, it is necessary to distinguish between intraarterial, intravenous, intramuscular, subcutaneous, and other routes.

6 APPLICATION FOR A VARIATION

In accordance with Directive 81/851/EEC, a marketing authorization for a veterinary medicinal product is granted for a period of five years, renewable upon application at least three months before expiry. Throughout the life of a veterinary medicinal product, the holder of the authorization is responsible for the product which circulates in the marketplace and is also required to take into account technical and scientific progress, and to make any amendments that may be required to enable the product to be manufactured and checked by means of generally accepted scientific methods. Such amendments must be approved by the competent authority prior to their introduction.

Marketing authorization holders may, in addition, wish to alter/improve the veterinary medicinal product or to introduce an additional safeguard during the period of five years. Such changes or 'variations' may involve administrative and/or more substantial changes, and speedy and efficient procedures for the approval of such changes, without jeopardising animal or public, have been set out in the Regulations on variations.

6.1 Regulations on variations

With the implementation of the new system of authorisation, the need was identified to categorise variations and to set out common procedures which, on the one hand facilitate the task of both industry and authorities and on the other hand, guarantee that changes to the veterinary medicinal product do not give rise to public or animal health concerns or concerns for the environment.

Express provisions have therefore been set out in two Commission regulations

- Regulation (EEC) No XX/95 of the Commission of x.x.1995 concerning the examination of variations to the terms of a marketing authorization granted by a competent authority of a Member State in a mutual recognition procedure;
- Regulation (EEC) No XX/95 of the Commission of x.x.1995 concerning the examination of variations to the terms of a marketing authorization granted in accordance with Council Regulation (EEC) No. 2309/93.

The operational procedures for these regulations are set out in Chapter II for marketing authorizations granted by a competent authority of a Member State in amutual recognition procedure and in Chapter IV for marketing authorization granted in accordance with Council Regulation (EEC) No. 2309/93.

6.2 Urgent Safety Restrictions

The Regulations do not impede the marketing authorization holder from taking provisional urgent safety restrictions in the event of risk to animal or public health or the environment. In such cases, the marketing authorization holder shall forthwith inform the appropriate competent authority/ Agency. If the competent authority/Agency has not raised any objections within 24 hours, the urgent safety restrictions may be introduced and the corresponding application for approval of the variation shall be submitted without delay.

Urgent safety restriction is defined as an interim change to product information by the marketing authorisation holder restricting the indication(s), and/or dosage, and/or target species of the product; or adding a contra-indication, and/or warning due to new information having a bearing on the safe use of the product.

6.3 Labelling changes

Changes to an aspect of the labelling or package inserts of veterinary medicinal products connected with the summary of product characteristics follow the procedure foreseen for variations - Type I or II as appropriate.

6.4 Manufacturing changes

The manufacture, both total or partial, of a veterinary medicinal product is subject to a manufacturing authorisation. In order to obtain a manufacturing authorization, the applicant must provide particulars in support of the application:

a) specify the veterinary medicinal products and pharmaceutical forms which are to be manufactured or imported and also the place where they are to be manufactured and/or controlled;

b) have at his disposal, for the manufacture or import of the above, suitable and sufficient premises, technical equipment and control facilities complying with the legal requirements;

c) have at his disposal the services of at least one qualified person within the meaning of Article 29 of Directive 81/851/EEC as amended.

The time taken for the procedure for granting the manufacturing authorisation does not exceed 90 days from the day on which the competent authority receives the (valid) application.

For changes requested by the manufacturer to any of the particulars in a) or b) above, the time taken for the procedure relating to the request shall not exceed 30 days. In exceptional cases this period may be extended to 90 days.

Should there be a requirement for further information from the applicant, the time limits shall be suspended until the additional data required has been supplied.

7. APPLICATION FOR RENEWAL

According to Council Directive 81/851/EEC, Article 15, a marketing authorization shall be valid for five years and be renewable for five-year periods upon application by the holder at least three months before expiry.

Not later than three months before the end of five years, the marketing authorization holder an application for renewal of the marketing authorization, including all currently approved presentations.

Before the procedure of renewal of a marketing authorization starts, the holder is advised to liaise with the competent authority/Agency concerning relevant documentation and timetable.

Only in special cases will it be acceptable to proceed with a variation for a product within a short time of the renewal application.

See Chapter II for renewals of marketing authorization granted following an opinion of the CVMP in accordance with Article 4 of Directive 87/22/EEC (concertation procedures).

8. PRESENTATION OF THE APPLICATION

The application dossier, which should be submitted in either a Community or national procedure, consists of administrative information and the necessary demonstration of quality, safety and efficacy of the product.

For non-immunological products, this is presented in four Parts:

Part I - Summary of the dossier

Part II - Chemical/pharmaceutical/biological documentation

Part III - Safety and residues documentation, including the environment

Part IV - Pre-clinical and clinical documentation.

For immunological products, this is presented in five Parts:

Part I - Summary of the dossier

Part II - Chemical/pharmaceutical/biological documentation, including the GMO information where relevant

Part III - Safety documentation

Part IV - Efficacy documentation

Part V - General conclusions

8.1 Part 1

Part I is divided into 3 sub-sections:

- Part IA consists of the administrative data, samples, manufacturing and marketing authorizations applied for or obtained elsewhere. A harmonised format for Part IA has been agreed by the competent authorities of the Member States and is reproduced in Chapter VII.
- Part IB consists of the proposed Summary of Product Characteristics (SPC), in accordance with Article 5a of Directive 81/851/EEC, as well aas the package insert, labelling, packaging and mock-ups. The guideline on the presentation of the SPC is reproduced in Chapter VII.
- Part IC consists of the Expert Reports and Annexes

Parts IA and IB must be in the language(s) of the Member State concerned or in all Community languages for centralised applications.

8.2 Invented name (Brand name)

Member States grant a marketing authorization to a single authorization holder who is responsible for placing the veterinary medicinal product on the market. The marketing authorization includes when available the INN (International Non-Proprietary Name) and when branded, a single invented name (brand name). In cases where companies wish to use

a second brand name, then a second authorization (perhaps using Article 5.10 a) i) must be submitted.

This principle will be applied similarly in the case of Community authorizations granted following applications through the centralised procedure.

It is important therefore, that applicants identify a brand name which would be valid throughout the Community when proposing to use the centralised procedure.

For applications through the mutual recognition procedures, it is recommended that the same brand name for a given medicinal product should be used in all Member States. If a different brand name is to be used, it should be quoted in a covering letter from the applicant to the competent authority giving the justification for the different name.

8.3 Technical documentation

Parts II, III, and IV of the application dossier consist of the chemical, pharmaceutical and biological documentation; the safety documentation and the efficacy documentation respectively, in accordance with the requirements of Directive 81/852/EEC.

8.4 GMO medicinal products

An application for marketing authorisation must be accompanied by the particulars and documents referred to in Article 5 of Directive 81/851/EEC as amended and in the Annex to Directive 81/852/EEC. In the case of a veterinary medicinal product containing or consisting of genetically modified organisms, the application must also be accompanied by

i) a copy of any written consent or consents of the competent authorities to the deliberate release into the environment of the genetically modified organisms for research and development purposes where provided for by Part B of Directive 90/220/EEC,

ii) the complete technical dossier supplying the information requested in Annexes II and III to Directive 90/220/EEC and the environmental risk assessment resulting from this information; the results of any investigations performed for the purposes of research or development.

The presentation of particulars concerning the environmental risk assessment for veterinary medicinal products which contain, or consist of, genetically modified organisms should be included in Part IIH of the dossier, as a separate (detachable) section.

From 1.1.95, applications for marketing authorizations should include in Part IIIR an indication of any potential risks presented by the veterinary medicinal product for the environment (see Chapter VI).

9. EXPERT REPORTS IN THE APPLICATION DOSSIER

9.1 General principles

Directive 81/851/EEC as amended requires that the particulars and documents submitted in the application dossier are drawn up and signed by experts, with the necessary technical or professional qualifications. The chemical/pharmaceutical/biological, safety and efficacy parts of the dossier should each include an Expert Report. In the case of a veterinary

medicinal product for food-producing animals, the safety expert repport should discuss, in addition to safety for the target species, the safety for consumers. Moreover, a specific Expert Report on the depletion of residues studies and, where appropriate, on the analytical methods proposed and the adequacy of the proposed withdrawal period(s) is also necessary. The Expert Reports, their tabular formats and eventual written summaries are placed in Part IC of the dossier.

It is important to emphasise that well prepared Expert Reports greatly facilitate the task of the competent authority in evaluating the dossier and contribute towards the speedy processing of applications. For these reasons particular care should be taken in the preparation of Expert Reports, following the guidance on the preparation of Expert Reports given in the 1993 edition of Volume VB.

Where relevant Community guidelines on the conduct of tests, studies and trials on a veterinary medicinal product exist, these should be taken into consideration when Expert Reports are prepared. Any deviation from guidelines should be discussed and justified. In particular, the experts should give a justification for the statements in the proposed SPC, taking into account the submitted data and the SPC guideline and also considering the need for bioavailability studies with reference to the guideline on bioavailability and bioequivalence in Volume VII.

An Expert Report for each of Parts II, III, IV is required for all types of applications, i.e. full and abridged (including hybrid) applications.

9.2 Expert Reports for abridged applications

As appropriate, Expert Reports may be abbreviated for an abridged (or amendment) application.

9.2.1 Consent from the marketing authorization holder

For applications based upon Article 5.10 (a)(i) of Directive 81/851/EEC, the Expert Reports of the original marketing authorization holder may be used.

9.2.2 Bibliographical applications

For applications based upon Article 5.10 (a)(ii) of Directive 81/851/EEC, the Expert Reports should particularly focus on the following elements:

a. the grounds for using published references and the relevance of the references selected

b. an update of published literature relevant to the substance and the present application. The expert may annotate review articles published in "peer review" journals, which may be acceptable in this respect.

c. a summary of impurities present in batches of the active substance (and, where relevant, decomposition products arising during storage) as proposed for use in the product to be marketed.

d the issue of bioavailability, and bioequivalence where appropriate, related to the proposed formula for marketing should be addressed taking into account the relevant pharmacokinetic parameters of the formulation used in the literature.

e. comparison of pharmacokinetic parameters (Cmax, Tmax, AUC etc.) of the formulations used in the literature and the formulation proposed for marketing;

f. for food-producing animals, relevance of the published data must be evaluated in comparison to the product formulations used (dosage, site of application, route of administration, etc)

g. an evaluation of the results of additional studies to provide for missing data in the file. These data should be discussed in the perspective of what is known from published literature. Additional studies should also be submitted in tabular formats provided in the Notice to Applicants;

h. every claim in the Summary of Product Characteristics (SPC) not known from or inferred from the properties of the veterinary medicinal product and/or its therapeutic group should be discussed in the Expert Reports and substantiated by published literature and/or additional studies.

9.2.3 Product essentially similar to a product authorised for 6 or 10 years

For applications based upon Article 5.10 (a)(iii) of Directive 81/851/EEC, the Expert Reports should particularly focus on the following elements:

a. the grounds for claiming essential similarity

b. a summary of impurities present in batches of the active substance (and where relevant decomposition products arising during storage) as proposed for use in the product to be marketed

c. an evaluation of the bioequivalence studies or a justification why studies were not performed with respect to the note for guidance on 'Investigation of Bioavailability and Bioequivalence' (Volume VII)

d. an update of published literature relevant to the substance and the present application. It may be acceptable for articles in "peer review" journals to be annotated for this purpose

e. every claim in the Summary of Product Characteristics (SPC) not known from or inferred from the properties of the veterinary medicinal product and/or its therapeutic group should be discussed in the Expert Report and substantiated by published literature and/or additional studies.

9.2.4 Extensions

For applications based on annex 2 of the regulations on variations, an application for a new marketing authorization must be made.

The Expert Report should particularly focus on the following elements:

a. an evaluation of the results of the additional studies. The results should be discussed in the perspective of what is known from published literature and previous submissions. Additional studies should also be submitted as required by the 1993 edition of Volume VB.

b. an update of published literature relevant to the substance and the present application. The expert may annotate articles published in "peer review" journals, which may be acceptable for this purpose.

c. every claim in the Summary of Product Characteristics (SPC) not known from or inferred from the properties of the medicinal product and/or its therapeutic group should be discussed in the Expert Report and substantiated by published literature and/or additional studies.

10. WRITTEN SUMMARY

A written summary may be of use, particularly for large application files. Applicants are therefore encouraged to include (systematically) a written summary in the following applications:

- new active substances;
- abridged applications where the demonstration of well established veterinary use, with recognised efficacy and an acceptable level of safety, relies on detailed references to published scientific literature;
- other abridged applications where, in the opinion of the applicant, the volume and complexity of the documentation would be such that a written summary would be helpful.

The written summary should be factual, complete (i.e. covering all studies) and concise. It should contain cross-references to the documentation in the relevant part of the dossier as well as including tables, graphs, etc.

It is important to avoid duplication and repetition between the Expert Report and the written summary. Equally, experience has shown that a good tabular presentation with a short written summary is an effective method of communication. Therefore, where tabular formats suffice, it is not necessary to duplicate the message in writing.

11. MAXIMUM RESIDUE LIMITS (MRLS) FOR NEW PHARMACOLOGICALLY ACTIVE SUBSTANCES

Directive 81/851/EEC provides that no veterinary medicinal product intended for administration to food-producing animals whose flesh or products are intended for human consumption may be authorised unless:

- the active substance or substances capable of pharmacological action contained in the veterinary medicinal product were authorised for use in other veterinary medicinal products in the Member States concerned on 1.1.1992;
- the active substance or substances capable of pharmacological action is or are mentioned in Annex I, II or III to Regulation (EEC) Nr. 2377/90.

Currently, there are two ways of proceeding in order to obtain an MRL for a new pharmacologically active substance:

a) to include the MRL file in the application for marketing authorisation for a veterinary medicinal product; in this case, the MRL documentation must be presented in separate volumes, which physically can stand alone and which can be handled separately from the remainder of the dossier;

b) to present the MRL file separately in advance.

In both instances, the file shall be presented as set out in Volume VI of The Rules governing Medicinal Products in the European Union.

It should be noted that, as from 1 January 1997, Article 4.2 of Directive 81/851/EEC provides that the Member States shall not permit foodstuffs for human consumption to be taken from test animals unless MRLs have been established by the Community in accordance with the provisions of Regulation (EEC) Nr. 2307/90 and an appropriate withdrawal period has been established to ensure that this maximum limit will not be exceeded in foodstuffs. The MRL file shall then always be presented in advance.

In accordance with Regulation (EEC) Nr. 2309/93, veterinary medicinal products intended for food-producing animals containing a new active substance which was not authorised in any Member State for use in food producing animals on 1 January 1995 benefit of List B status, i.e. optional use of the centralised procedure.

The establishment of MRLs being a Community procedure, the MRL file shall be submitted to the EMEA, also if the decentralised procedure is chosen by the applicant for the veterinary medicinal product concerned. The file shall fulfill the provisions set out in Volume VI.

When the application is made, one copy of the file is to be forwarded to the Agency for the validation period. At its next meeting, the CVMP will appoint or confirm the rapporteur and the co-rapporteur, who should then receive one copy each. At this stage the CVMP also determines if any of its members should receive an extra copy.

Thirty-four (34) copies of Expert Reports (Residue & Safety) should be prepared. They are to be distributed as follows: four copies are to be forwarded to the EMEA at the time the full dossier is submitted. Once the dossier has been validated by the EMEA, one copy should be sent to each member of the CVMP.

CHAPTER II

MUTUAL RECOGNITION

1 LEGAL BASIS AND PURPOSE

As of 1 January 1995, a pharmaceutical company wishing to market a veterinary medicinal product in more than one Member State can avail of mutual recognition. This can be achieved by asking the second or subsequent Member State to mutually recognise, within 90 days, the marketing authorisation granted by the reference Member State.

Equally, Member States may benefit from the assessment of another Member State by mutual recognition even in cases where the company has not requested mutual recognition with its application. Again a period of 90 days applies.

Thus rapid access to a single market, with the necessary safeguards for the protection of public health, can be obtained using the principle of mutual recognition, either at the request of the pharmaceutical company or the Member States.

From 1 January 1998, Member States must mutually recognise a marketing authorisation granted by another Member State, also within 90 days.

The legal texts setting out the mutual recognition procedures are in Directives 81/851/EEC and 81/852/EEC as amended.

The objective of these Community procedures is to facilitate access to a single market by relying upon the principle of mutual recognition. Thus with the exception of those veterinary medicinal products which are subject to the centralised Community authorisation procedure established by Council Regulation (EEC) No. 2309/93 of 22 July 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products, an authorisation to place a medicinal product on the market in one Member State ought in principle to be recognised by the competent authorities of the other Member States (unless there are serious grounds for supposing that the authorisation of the medicinal product concerned may present a risk to human or animal health or the environment)[1].

The procedure may be initiated either by the person responsible for placing the medicinal product on the market or by a Member State.

In addition to a speedy procedure, mutual recognition has been reinforced by two important new elements:

* a Member State should be able to suspend the examination of an application for authorisation to place a veterinary medicinal product on the market which is currently under examination in another Member State with a view to recognising the decision reached by the latter Member State.
* in the event of a disagreement between Member States about the quality, the safety or the efficacy of the veterinary medicinal product, a scientific evaluation of the matter should be undertaken by the Committee attached to the European Agency for the Evaluation of

[1] *The expression "risk to human or animal health or the environment" refers to the quality, safety and efficacy of the veterinary medicinal product.*

Medicinal Products, leading to a single decision in the area of disagreement, binding on the Member States.

2. SCOPE

2.1 Applications eligible for the mutual recognition procedure.

The mutual recognition procedure may be used for full applications and abridged applications. Once the procedure has been used, all variations to these veterinary medicinal products must use the mutual recognition procedure (cf. Commission Regulation XX/95). In addition, variations to previous concertation products authorized by Member States following an opinion of the Committee given before 1 January 1995 are required to use the procedure set out in the Commission Regulation XX/95 (these applications "convert" to the mutual recognition procedure, see Commission Communication of 19.3.94 O.J. Nr. C82).

2.2 Repeat use

The mutual recognition procedure may be used more than once for a subsequent application made to another Member State in relation to the same veterinary medicinal product. In such cases, the application would comprise a dossier and a proposal for a SPC identical to that which had been authorised by earlier Member States. However, such subsequent applications may give rise to grounds for supposing risk(s) to human or animal health or the environment different from those which may have been considered in an earlier procedure. Should a risk for human or animal health or the environment lead to arbitration, all Member States where the veterinary medicinal product is authorised or an application is pending, would be concerned. **For this reason it is recommended that, wherever feasible, persons responsible for placing the veterinary medicinal product on the market seek to involve all Member States (where it is already on the market or where it is envisaged that the product will eventually be marketed) in the first usage of the mutual recognition procedure and thus avoid potential repeated arbitrations on human or animal health or environment issues.**

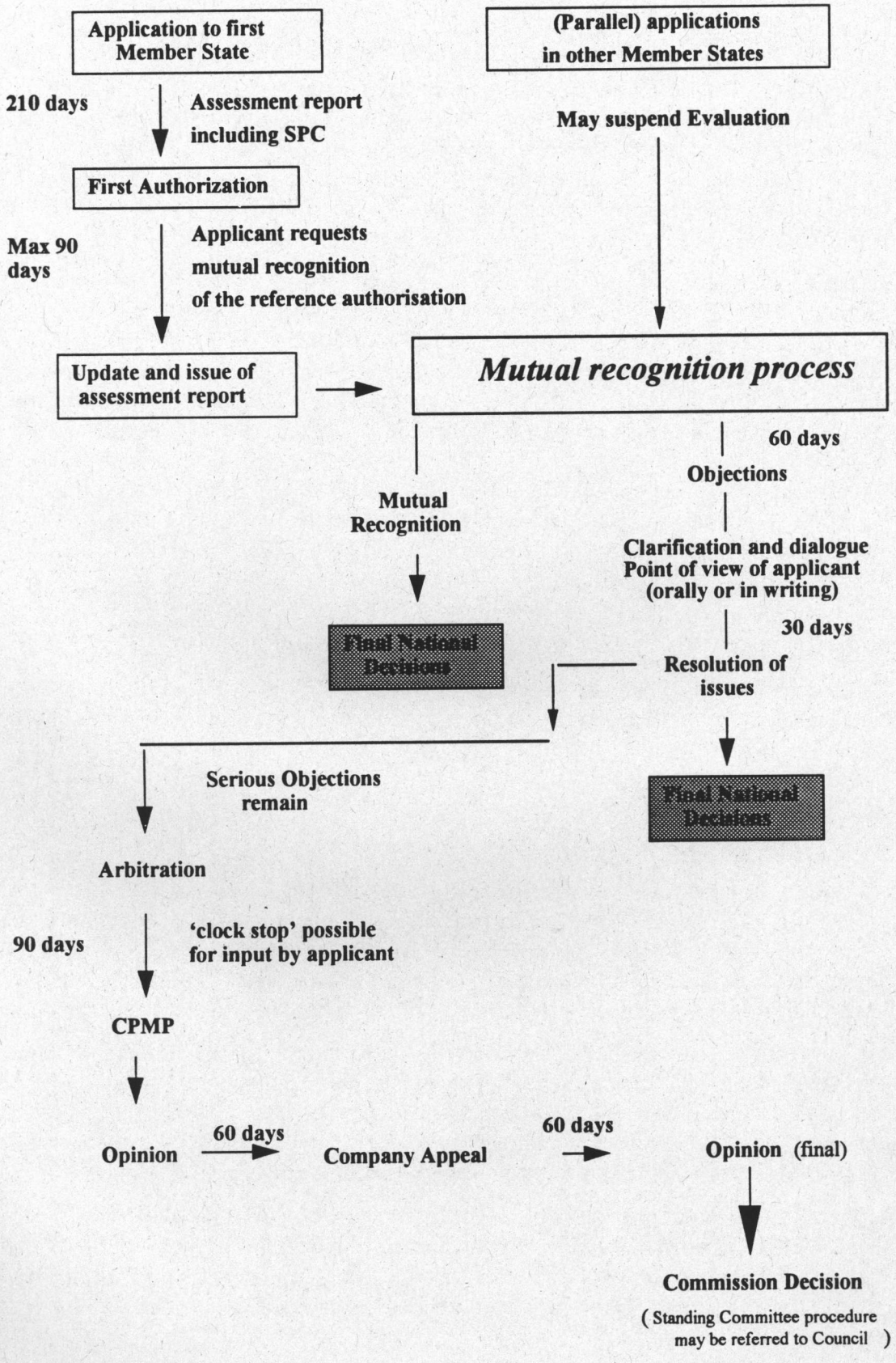
2.3 Exclusions

The procedure is not appropriate for applications submitted through the centralised (Part B) procedure, or for applications in respect of products developed by one of the biotechnological processes listed in Part A of the Annex to Council Regulation (EEC) No. 2309/93, **except** in the case of applications which were made in accordance with List A or List B of Directive 87/22/EEC as amended, for which the CVMP had before 1 January 1995 issued an opinion.

The procedure is not appropriate for variations to veterinary medicinal products which had not already been considered through the mutual recognition procedures or had not been authorised by Member States following an opinion of the Committee given before 31 December 1994 in accordance with Article 4 of Directive 87/22/EEC.

The procedure is not appropriate for medicinal products which have not yet been authorised according to all relevant Community Directives and guidelines (e.g. immunological veterinary medicinal products which have not yet been authorised in accordance with the directives; up to March 1998).

Mutual recognition procedure(s)



According to Article 14.5 of Directive 75/319/EEC as amended the procedure is not foreseen for homoeopathic veterinary medicinal products for human use authorized according to Article 9.2 of Council Directive 92/74/EEC.

2.4 Maximum Residue Limits for veterinary medicinal products

In the case of a veterinary medicinal product intended for use in food producing animals, Regulation (EEC) No. 2377/90 must be taken into consideration. If the pharmacologically active substance concerned is not inserted in Annex I, II or III of Regulation (EEC) No. 2377/90 as amended, the person responsible for placing the product on the market has to verify, as early as possible, whether the substance has been authorised before the 1.1.1992 by the Member State(s) concerned for use in the food producing animals concerned.

If the substance has not been authorised before the 1.1.1992 for use in food producing animals in the Member State concerned, an application for the establishment of the Maximum Residue Limit (MRL) for the active substance should be made to the EMEA either before or at the same time as an application for marketing authorisation is made to the Member State(s) concerned. However, in order to avoid any unnecessary delay in the evaluation, the persons responsible for placing the product on the market are strongly advised to submit an application for the establishment of MRLs as soon as the relevant documentation is ready, before an application for marketing authorisation is submitted to the Member State(s) concerned. In this case the 90 day period for the concerned Member State(s) starts after the substance has been inserted into Annex I, II, or III of Regulation (EEC) No. 2377/90.

3. PROCEDURES LEADING TO MUTUAL RECOGNITION

The procedure to be followed will depend upon whether it is a Member State or the person responsible for placing the medicinal product on the market which initiates it.

3.1 Initiation by a Member State

3.1.1 Suspension of detailed examination

Where a Member State is informed that an application for authorisation submitted after 1 January 1995 is already under active examination in another Member State in respect of that veterinary medicinal product, the Member State concerned may decide to suspend the detailed examination of the application in order to await the assessment report prepared by the other Member State in accordance with Article 5b of Directive 81/851/EEC as amended.

In such cases, the Member State concerned shall inform the other Member State and the person responsible for placing the veterinary medicinal product on the market of its decision to suspend detailed examination of the application in question. As soon as it has completed the examination of the application and reached a decision, the other Member State shall forward a copy of its assessment report to the Member State concerned.

Where a Member State receives a notification under point 13 of Article 5 of Directive 81/851/EEC as amended for veterinary medicinal products that another Member State has authorized the product in question, that Member State may request the assessment report from the reference Member State which has authorised the veterinary medicinal product.

Within 90 days of the receipt of the assessment report, the Member State concerned shall normally recognise the decision of the other Member State and the summary of the product characteristics as approved by it (by granting a marketing authorisation with an identical summary of the product characteristics).

Only in exceptional circumstances, where a Member State considers that there are grounds for supposing that the authorisation of the medicinal product concerned may present a risk to human or animal health or the environment, the Member State shall apply the procedures set out in Articles 18 to 22 of Directive 81/851/EEC as amended (see Chapter III).

The introduction of the possibility for Member States to suspend their detailed examination in order to await the assessment report of another Member State, allows efficient utilisation of resources and the avoidance of duplication of effort. Member States may use this possibly during the transition period from 1 January 1995 to 1 January 1998, and after the transition period for applications which are submitted in parallel to Member States for veterinary medicinal products for which a marketing authorisation has not yet been granted.

3.1.2 Automatic mutual recognition

With effect from 1 January 1998, where a Member State is informed in accordance with point 13 of Directive 81/851/EEC as amended that another Member State has authorized a veterinary medicinal product which is the subject of an application for authorisation in the Member State concerned, that Member State shall forthwith request the authorities of the Member State which has granted the authorisation to forward to it the assessment report referred to in Article 5b of Directive 81/851/EEC as amended.

Within 90 days of the receipt of the assessment report, the Member State concerned shall normally recognise the decision of the first Member State and the summary of the product characteristics as approved by it (by granting a marketing authorisation with an identical summary of the product characteristics), or, if it considers that there are grounds for supposing that the authorisation of the veterinary medicinal product concerned may present a risk to human or animal health or the environment, it shall apply the procedures set out in Articles 18 to 22 of Directive 81/851/EEC as amended.

3.2 Initiation by the person responsible for placing the veterinary medicinal product on the market

The person responsible for placing the veterinary medicinal product on the market may request one or more Member States to mutually recognise an authorisation granted by a reference Member State. An application is submitted to the competent authorities of the Member State or Member States concerned, together with the information and particulars referred to in Articles 5, 5a, 5b of Directive 81/851/EEC as amended. The person responsible for placing the veterinary medicinal product on the market must give an assurance that the dossier is identical to that accepted by the first Member State, or identify any additions or amendments it may contain. In the latter case, he must give an assurance that the summary of the product characteristics proposed by him in accordance with Article 5a of Directive 81/851/EEC as amended is identical to that accepted by the reference Member State in accordance with Article 5b of Directive 81/851/EEC as amended. Moreover he shall certify that all the dossiers filed as part of the procedure are identical.

3.2.1 Discussion with the reference Member State

Before submitting an application under the mutual recognition procedure, the person responsible for placing the veterinary medicinal product on the market must inform the reference Member State that such an application is to be made.

The person responsible for placing the veterinary medicinal product on the market is in any case **advised** to discuss, in advance, the proposed mutual recognition application with the reference Member State, especially if the authorisation was granted some time previously. Such discussion would include whether the dossier and Expert Reports should now be updated to ensure that all relevant information is supplied (according to current requirements, legislative and technical aspects). The reference Member State may require the person responsible for placing the veterinary medicinal product on the market to provide reassurance that the dossier submitted in other Member States is identical to that upon which it took its own decision.

When a national application is first submitted in a Member State with a view to subsequently requesting mutual recognition of the authorisation in other Member States, it is advantageous if this is known to the reference Member State at the time so that advice and counsel can be given. This would also facilitate the availability of the assessment report within a very short period after the grant of the authorisation in a language understood in the concerned Member States.

For completeness of information, the person responsible for placing the product on the market is advised to also inform other Member States of the application for mutual recognition, particularly where the veterinary medicinal product is already authorised.

3.2.2 Updating the dossier and expert report (if necessary.)

As indicated under 3.2.1, the application should be updated, if necessary, according to current requirements, both legal and technical (including CVMP guidelines).

In addition, the dossier and Expert Reports should be updated to bring them into line with the changes agreed during the assessment with the reference Member State in an appropriately updated dossier. In particular, the Expert Reports should include a comment or justification for the proposed wording of the Summary of Product Characteristics.

3.2.3 Assessment Report

As stated previously, it is preferable for the person responsible for placing the veterinary medicinal product on the market to give the reference Member State advanced notice of the intention to use the marketing authorisation in the mutual recognition procedure. In any event, the person responsible for placing the medicinal product on the market must request the reference Member State in writing to supply an (up-dated) assessment report. This is to be furnished as soon as possible, and not later than 90 days after the receipt of the request. Normally the assessment report prepared during the initial assessment will be available, but the reference Member State may need the 90 days to update it. The report would include an appropriate assessment of variations and any additional information bearing upon safety or efficacy reported since the authorisation had been granted. The reference Member State will

notify the person responsible for placing the veterinary medicinal product on the market when the report is/will be available.

There is no obligation upon the Member State to make the assessment report available to the applicant. Where it is made available to the company, the other concerned Member States will be informed. In any event, the assessment report remains a confidential document, and further publication or distribution to other parties, either in whole or in part, is subject to the written agreement of the competent authority.

Arrangements for translation will be made by the reference Member State, but the costs of translation are borne by the person responsible for placing the veterinary medicinal product on the market.

3.2.4 Before submitting the application:

The person responsible for placing the veterinary medicinal product on the market must ensure that:

(a) the application is updated to current requirements (i.e. in accordance with Directives and Committee guidelines issued after the original marketing authorisation was granted);

(b) that the product will be regarded as a veterinary medicinal product in all concerned Member States (and that it will not be regarded, for example, as a dietary supplement, a medical device or pesticide);

(c) the veterinary medicinal product has been reviewed in accordance with the requirements of the Directives;

(d) the clinical indications sought have either been previously authorised (and as appropriate submission of clinical data is exempted by the provisions of the Directives) for a veterinary medicinal product containing the same active substance in the concerned Member States or, if not, that adequate clinical data is available to support the claimed indications in the Summary of Product Characteristics;

(e) the requirements for "essential similarity" for abridged applications under Article 5(10)(a)(iii) of Directive 81/851/EEC as amended, have been met, i.e. that there is a veterinary medicinal product authorized in the EC more than 6 or 10 years previously and such a product is marketed in the concerned Member States;

(f) in the case of active substances which may have been authorised in some Member States and not in others or, with regard to veterinary products, in different relevant target species, additional documentation will have to be provided for those Member States which have not previously authorised the active substance or its use in the target animals concerned;

(g) variations to the original authorisation have been authorised by the reference Member State in advance of the initiation of the procedure; and,

(h) the final text of the approved Summary of Product Characteristics and that of the package insert for information, in the national language of the reference Member State should be available, with appropriate translations.

3.3 Making the application

The person responsible for placing the veterinary medicinal product on the market must submit an application to the competent authorities of each of the Member States wherein a marketing authorisation is to be sought (i.e. the "concerned Member States").

The person responsible for placing the veterinary medicinal product on the market is required to give an assurance (usually in the covering letter accompanying the application) that;

- the dossier is identical (including any approved variations) to that accepted by the reference Member State, or to identify any additions,
- the SPC is identical, and
- the dossier and SPC as submitted are identical in all concerned Member States.

The dossier must include the EC Application Form Part 1A.

The appropriate national fees need to be paid (names and addresses for fees enquiries and details of how payments are to be made are set out in Chapter VII).

In some Member States, there may be different addresses for submission of the dossier and for correspondence in connection with an application (see Chapter VII).

It is not part of the responsibility of the competent authorities to arrange customs clearance of applications. It is the responsibility of the person responsible for placing the veterinary medicinal product on the market to deliver the application to the officially designated address, free of any charges to the addressee.

Reference Member States will indicate (during the discussion mentioned in 3.2.1 above) what documentation they require when they are the reference Member State. A copy of the application should be available to be sent to the reference Member State on request.

3.3.1 Number of copies required and languages.

The numbers of copies of the dossier and required languages of the Member States to be used are set out in Chapter VII. Copies of the SPC, label and leaflet texts are always needed in the national language(s).

Requirements of each Member State for samples of the active substance and finished dosage form are set out in Chapter VII.

3.4 Notification to the Committee

At the time of making the application, the person responsible for placing the veterinary medicinal product on the market must also notify the Committee.

The following information should be included in the notification:-

- the names of the concerned Member States and the dates the application has been submitted in each Member State;
- a copy of the authorisation granted by the reference Member State;
- copies of any marketing authorisations already granted by other Member States;
- status of any application(s) currently under consideration in any Member State;
- name and address of the person responsible for placing the veterinary medicinal product on the market, i.e. the marketing authorisation holder in the reference Member State;
- name and address of the person responsible for placing the veterinary medicinal product on the market in each of the concerned Member States;
- the INN name of the active ingredient(s) in the veterinary medicinal product;
- the ATC/Vet code;
- the trade name(s) of the products in the concerned Member State(s);
- the mutual recognition procedure number [details to be announced later] for administrative handling (marketing authorisation numbers are given by the Member States concerned).

3.5 Action following the submission of the Application

The application is checked in by the concerned Member States using the check-in procedure in Chapter VII. Any problems are notified immediately (by telefax or E-mail to the person responsible for placing the veterinary medicinal product on the market and the reference Member State). The concerned Member States will notify within 10 days, by telefax or E-mail, the reference Member State and the person responsible for placing the veterinary medicinal product on the market that a valid application together with the reference Member State's assessment report has been received.

After all of the concerned Member States have confirmed receipt of the valid (checked in) application and the reference Member State's assessment report, the reference Member State notifies all Member States and the person responsible for placing the veterinary medicinal product on the market of the start of the 90-day period referred to in Article 17.4 of Directive 81/851/EEC as amended.

3.6 Recognition of the original authorisation

Normally, in accordance with Article 17.4 of Directive 81/851/EEC as amended, each Member State concerned will recognise the marketing authorisation and the SPC granted by the reference Member State and grant the national authorisation within the 90 days period. They will inform the reference Member State, the other concerned Member States, the Committee and the person responsible for placing the veterinary medicinal product on the market.

3.7 Mutual recognition of the SPC

In accordance with article 18.2 of Directive 81/851/EEC, as amended by Directive 93/40/EEC, "all Member States concerned shall use their best endeavours to reach agreement on the action to be taken in respect of the application" submitted for mutual recognition. Therefore in order to maximise the efficiency of this clarification and dialogue stage, Member States have agreed the following three-step procedure:

Step 0 :

Before initiation of the Mutual Recognition Procedure the Reference Member State (RMS) is requested to achieve an 'acceptable' Summary of Product Characteristics (SPC) through discussion with the applicant, which would take into account all existing national SPCs.

It is expected that through this updating process harmonisation can be achieved concerning "core" issues and also additional issues.

Both the RMS and the applicant are expected to react in a flexible manner.

Step 1 :

During the Clarification and Discussion phase (90 days) :

a) the Reference Member State, having liaised with the applicant, would be flexible;

b) discussion would concentrate on
   - target species
   - indications
   - dosage
   - contra-indications
   - shelf-life
   - withdrawal periods
   - user safety

   Concerned Member State(s) would forward, in writing and within 60 days, their concerns and alternative wordings for the sections which cause concern.

c) the remainder of the SPC of the RMS would be mutually recognised.

Step 2 :

When necessary, and in cases where the remainder of the SPC is requested to be harmonised by the RMS i.e. development of a common SPC, the competent authorities of those Member States requesting SPC changes will meet, and try to define the necessary changes. This would be achieved through special liaison, using phone, fax, e-mail etc. and other face-to-face opportunities (e.g. meeting rooms in EMEA).

In the event that consensus on one or more sections was not possible, the text of the RMS would be used.

Such liaison would result in 'the' draft SPC.

The draft SPC is then circulated to all competent authorities for comment within 10 days.

'The' SPC (for the veterinary medicinal product which is the subject of the mutual recognition procedure) would be presented to the CVMP for information.

The CVMP could use this SPC as a draft for the development of a (substance specific) Core-SPC.

To avoid duplication of work, normally, the CVMP will ask those experts who where involved in the discussions of 'the' SPC to continue their work as a drafting group until the "Core"-SPC is finalised. Other Member States are asked to support this Expert Group with the aim to achieve a generally acceptable European Core-SPC.

The mechanism of implementation of a harmonised SPC for veterinary medicinal products other than that directly concerned would also be considered.

It is pointed out that the SPC in question is only for the veterinary medicinal product dealt with in the Mutual Recognition Procedure. Other similar products, common to all or some Member States will not be addressed by this procedure, unless they differ only in details, e.g. same company, different strength.

Harmonisation across several veterinary medicinal products concerning the same active substance or across other issues of their SPC's would be addressed separately.

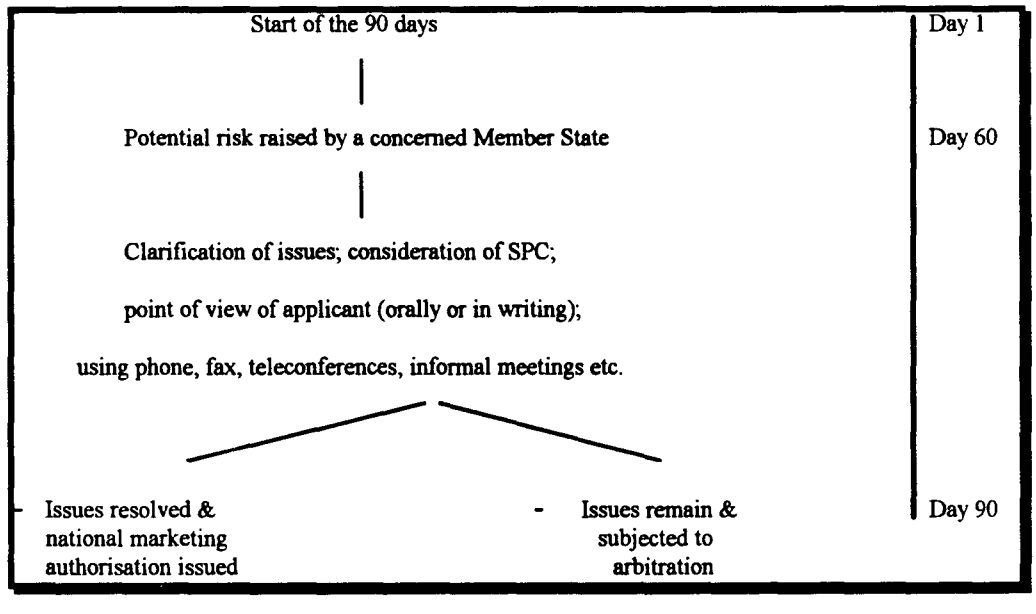
3.8 Maintenance of identicality of the dossier

Having the benefit of mutual recognition of the marketing authorisation also carries through the life of the veterinary medicinal product. Thus variations to a veterinary medicinal product which has benefited from mutual recognition, also benefit from a rapid mutual recognition procedure. In this way, a dossier which has been harmonised continues to be consistent and identical in all Member States where the veterinary medicinal product is authorised.

4. CLARIFICATION AND DIALOGUE

4.1 Operating procedure

Any concerned Member State which considers there may be a potential risk to human or animal health or the environment must notify the reference Member State, the other concerned Member States, the person responsible for placing the veterinary medicinal product on the market and the Committee. Detailed reasons must be given, together with the action considered necessary to correct any defect in the application. This should be done as soon as possible. Member States have agreed that, where concern regarding such a risk exists and in order to provide time for 'their best endeavours to reach agreement', such notification would take place within 60 days (by telefax, E-mail etc.) of the start of the 90 days referred to in Articles 8, 8a and 17 of Directive 81/851/EEC as amended.



Within this period, clarification of potential concerns and deficiencies would be carried out by dialogue (telephone/telefax/E-mail) between the reference Member State, the other concerned Member States and the applicant.

The person responsible for placing the veterinary medicinal product on the market will be given an opportunity to make his point of view known orally or in writing. Where a risk has been raised by only one of the concerned Member States, the person responsible for placing the veterinary medicinal product on the market is advised to liaise directly with that Member State in order to agree action to be taken in respect of the application, whilst keeping the reference and other concerned Member State(s) informed. If more than one concerned Member State raises concerns regarding risk(s) to human or animal health or the environment, direct liaison with individual Member States may lead to actions which would not be acceptable to other concerned Member States. Thus, for these cases, the person responsible for placing the veterinary medicinal product on the market is advised to liaise with the reference Member State as to the optimal mechanism for liason e.g. phone, fax, teleconference, E-mail or informal meetings. Different models will be explored and in the light of practical experience the best practice will evolve.

Normally the issues raised may be resolved and the marketing authorisation of the reference Member State can be recognised within the 90 day period set out in Articles 8, 8a and 17 of Directive 81/851/EEC as amended.

Where no issues in relation to risks to human or animal health or the environment remain, the concerned Member States will recognise the authorisation within 90 days of receipt of the application and assessment report, grant a national marketing authorisation and notify the

person responsible for placing the veterinary medicinal product on the market, the other concerned Member States and the Committee.

Note:

An application for a marketing authorisation may be withdrawn by the applicant at any time during the mutual recognition procedure. Thus an application may be withdrawn during examination by a competent authority, or during the mutual recognition procedure, including the clarification and dialogue phase. However, once an application has been submitted for arbitration, the opinion of the Committee will be given unless the veterinary medicinal product no longer exists (i.e. all applications and marketing authorisations are withdrawn).

4.2 Revision of the authorisation in the reference Member State.

Where, in the course of the procedure outlined in Article 18 of Directive 81/851/EEC as amended, changes have been agreed by the person responsible for placing the veterinary medicinal product on the market and the reference Member State to the authorisation of the reference Member State, these will be introduced using the appropriate procedure.

5. VARIATIONS TO A MARKETING AUTHORISATION

Throughout the life of a veterinary medicinal product, the holder of the authorisation is responsible for the product which circulates in the marketplace and is also required to take into account technical and scientific progress, and to make any amendments that may be required to enable the veterinary medicinal product to be manufactured and checked by means of generally accepted scientific methods.

Marketing authorisation holders may, in addition, wish to alter/improve the veterinary medicinal product or to introduce an additional safeguard during the period of five years.

Such changes or 'variations' may involve administrative and/or more substantial changes, and the procedures for the approval of such changes, without jeopardising public or animal health, have been set out in Regulation (EEC) No. XX/95.

The term variation is defined in Regulation (EEC) No. XX/95: "*an amendment to the contents of the documents referred to in Article 5 5a and 7 of Directive 81/851/EEC such as they existed at the moment the decision on the marketing authorisation or after approval of any previous variations, except where a new application for a marketing authorisation must be presented pursuant to Annex II of this Regulation*".

An application for a variation is submitted simultaneously to each of the competent authorities of the different Member States where the veterinary medicinal product is authorised, accompanied by the appropriate fee and documentation. Member States grant a marketing authorisation to one marketing authorisation holder. The marketing authorization holder may be located in that Member State or in another Member State. In cases where the same person/company holds the marketing authorisation in all Member States, the application for a variation will be submitted by that person/company. In cases where the marketing authorisation holder is not the same in all Member States, it is essential that the holders

synchronise the submission of the application for the variation. It is clear that a variation to a veterinary medicinal product which has been the subject of one of the mutual recognition procedures, must remain harmonised and that variations occur at the same time in all Member States where such a veterinary medicinal product is authorised.

In the Regulation XX/95 on variations to marketing authorization granted by the competent authorities of the Member States, the expression marketing authorization holder(s) is used. The use of the plural in this context is intended to cover situations where the marketing authorization holder is different in the different Member States - it must not be interpreted as signifying multiple holders of a single marketing authorization.

5.1 Urgent Safety Restriction

An urgent safety restriction is defined in Article 2.2 of Regulation (EEC) No. XX/95 as : "*An interim change to product information by the marketing authorisation holder restricting the indication(s), and/or dosage, and/or target species of the medicinal product; or adding a contra-indication, and/or warning due to new information having a bearing on the safe use of the product*".

The person responsible for placing the veterinary medicinal product on the market must immediately inform the Agency, the Commission and the Member States of any new information which might influence the evaluation of the benefits and risks of the veterinary medicinal product. In cases where the marketing authorisation holder is not the same in all Member States, it is essential that the holders co-ordinate any urgent action of the veterinary medicinal product (in Article 1.2 of Regulation XX/95, the reference to holder(s) is expressly to cover this type of situation).

In cases of urgency, where there is a risk to public or animal health or the environment, marketing authorisation holder(s) may make urgent safety restrictions in accordance with Regulation XX/95. These measures must be communicated without delay to the national competent authorities. If the national competent authorities have not raised any objections within 24 hours, the urgent safety restrictions may be introduced and the corresponding application for this variation (type II) shall be submitted without delay to the national competent authorities, for application of the procedures set out in Articles 6 and 7 of Regulation XX/95.

5.2 Extension applications

Changes which are fundamental and which as a consequence require new applications may be assimilated to an existing authorisation (including where relevant, the existing authorisation number) in accordance with the procedures operated by the competent authority of the Member States concerned.

5.3 Type I variations

A "minor variation" (type I) means a variation as defined in Article 2 and listed in Annex I to Regulation (EEC) No. XX/95, provided the conditions for such variation laid down in the Annex are met.

The procedure and documentation required for a type I variation are set out in the regulation. As an illustrative guide, the following procedure would generally be followed.

a) Initial application acceptable:

Application submitted simultaneously to the reference Member State and all other Member States where the veterinary medicinal product is authorised ↓ Concerned Member States notify receipt of application to the reference Member State ↓ Reference Member State informs concerned Member States and the marketing authorisation holder of the starting date of the procedure ↓ No objection raised by any concerned Member State ⇒ variation deemed to be accepted (without need for written confirmation)	Day 1 ↓ ↓ ↓ Day 30

b) Initial application not acceptable; marketing authorisation holder does not amend

Application submitted simultaneously to the reference Member State and all other Member States where the veterinary medicinal product is authorised	
↓	
Concerned Member States notify receipt of application to the reference Member State	
↓	
After the last concerned Member State notification has been received, the reference Member State informs concerned Member States and the marketing authorisation holder of the starting date of the procedure	Day 1
↓	
Objective grounds for non-acceptance raised by a concerned Member State and communicated to reference Member State	Day 20
↓	
Notification with grounds (i.e. refusal) sent by reference Member State to marketing authorisation holder, with copy to concerned Member States	Day 30
Marketing authorisation holder has 30 days to amend the application taking into account the objective grounds	+/- 30 days
↓	
If no response is received, the application is deemed to have been rejected	
↓	+/- 60 days
Reference Member State notifies rejection to other concerned Member States	

c)Initial application not acceptable; marketing authorisation holder does not amend

Application submitted simultaneously to the reference Member State and all other Member States where the veterinary medicinal product is authorised ↓ Concerned Member States notify receipt of valid application to the reference Member State ↓	
After the last concerned Member State notification has been received, reference Member State informs concerned Member States and the marketing authorisation holder of the starting date of the procedure	Day 1
↓ Objective grounds for non-acceptance raised by a concerned Member State and communicated to reference Member State	Day 20
↓ Notification with grounds (i.e. refusal) sent by reference Member State to marketing authorisation holder, with copy to concerned Member States	Day 30
↓ Marketing authorisation holder has 30 days to amend the application taking into account the objective grounds	Clock stopped for up to 30 days
↓ Amendment is submitted to reference Member State and all other concerned Member States	
↓ Concerned Member States notify their final position to the reference Member State	Day +/- 60

↓ Concerned Member States are unanimously favourable ⇒ variation deemed to be accepted	↓ Concerned Member States are unanimously unfavourable ⇒ variation is rejected, written rejection from reference Member State	↓ **Concerned Member States are divergent ⇒ variation is rejected, written rejection from reference Member State**	↓ **Day 70** **In cases of divergence, the marketing authorisation holder may refer the matter for arbitration**

5.4 Type II variations

A "major variation" (type II) means a variation which cannot be deemed to be a type I variation within the meaning of Article 2 of the Regulation and which does not require a new application.

a) Standard mutual recognition

<table>
<tr><td colspan="2">Application submitted simultaneously to the reference Member State and all other Member States where the veterinary medicinal product is authorised
↓
Concerned Member States notify receipt of the valid application to the reference Member State
↓
After the last concerned Member State notification has been received, Reference Member State informs concerned Member States and the marketing authorisation holder of the starting date of the procedure
↓
A single request for supplementary information may be made by the reference Member State. Other concerned Member States are informed of this request. Clock is stopped for up to 60 days, this period may be extended on the initiative of the reference Member State or at the request of the marketing authorisation holder.
↓
Reference Member State sends an assessment report and draft decision to other concerned Member States
↓
Other concerned Member States accept the draft decision and inform the reference Member State accordingly
↓ ↓</td><td>Day 1
↓
↓
↓
↓
Clock stopped
(+/- 60 days)
↓
↓
↓
Day 60
(+/- 60 days)
↓
Day 90</td></tr>
<tr><td>Variation (unanimously) approved ⇒
Reference Member State and marketing authorisation holder, in consultation with the other concerned Member States, agree the date of effect of the national decisions</td><td>Variation (unanimously) refused ⇒
All concerned Member States send written refusal to marketing authorisation holder</td></tr>
</table>

b) Divergent views between the Member States

Application submitted simultaneously to the reference Member State and all other Member States where the veterinary medicinal product is authorised ↓ Concerned Member States notify receipt of the valid application to the reference Member State ↓	
After the last concerned Member State notification has been received, Reference Member State informs concerned Member States and the marketing authorisation holder of the starting date of the procedure ↓	Day 1 ↓ ↓ ↓ ↓
A single request for supplementary information may be made by the reference Member State. Other concerned Member States are informed of this request. Clock is stopped for up to 60 days, this period may be extended on the initiative of the reference Member State or at the request of the marketing authorisation holder. ↓	Clock stopped (+/- 60 days) ↓ ↓ ↓
Reference Member State sends an assessment report and draft decision to other concerned Member States ↓	Day 60 (+/- 60 days) ↓ ↓
If other concerned Member States cannot mutually recognise the draft decision, the matter is referred for arbitration (see Chapter III, section 7)	Day 90

6. RENEWAL OF THE MARKETING AUTHORISATION

The renewal process should not be confused with the procedure for variations. They are independent procedures and operate for different purposes. The holder of the marketing authorisation is required to update the marketing authorisation throughout the life of the product, taking into account all new technical and scientific factors concerning quality, safety and efficacy and these updates are done through variations .

6.1 Scope

The text hereunder describes the agreed procedure for renewal of marketing authorisation granted by Member States following an opinion of the CVMP in accordance with Article 4 of Directive 87/22/EEC i.e. concertation procedure, before 31 December 1994 and which 'convert' to the mutual recognition procedure.

6.2 Period of validity of a marketing authorisation

According to Council Directive 81/851/EEC, a marketing authorization shall be valid for five years and be renewable for five-year periods upon application by the holder at least three months before expiry.

The date of authorisation by a Member State following a CVMP opinion on an application in accordance with Article 4 of Directive 87/22/EEC is used to calculate the starting date for the renewal.

6.3 Making the application for renewal

Not later than three months before the end of the five years after the first authorisation following the CVMP opinion on the veterinary medicinal product, the marketing authorisation holder should submit an identical application for the renewal of the marketing authorisation. This should be submitted simultaneously in all Member States where the veterinary medicinal product is authorised and where the holder wishes to renew the marketing authorisation

When renewals for other presentations of the same veterinary medicinal product fall within a period of +/- six months, the renewal for all presentations could be covered by a single renewal.

In support of the application for renewal, the following documentation should be submitted, together with the appropriate fee:

a) an updated Part IA, including current manufacturing authorisation;

b) a chronological list of all the variations of any type approved since the grant of the marketing authorisation or last renewal, including the CVMP opinion number and dates;

c) the required periodic safety updates including all the relevant pharmacovigilance data since the grant of the marketing authorisation;

d) update of studies requested in the CVMP opinion (if not already submitted);

e) brief update of quality according to the relevant guidelines;

f) the current SPC and a proposal for a harmonised SPC, if considered appropriate, together with an updated package insert and labelling text, taking into account applicable directives and guidelines.

6.4 Procedure

The documentation submitted is evaluated by the Member State which had acted as rapporteur during the concertation procedure on behalf of all Member States:

a) within 60 days following the receipt of the application, the reference Member State prepares a succinct assessment report and a draft decision (including the SPC) which is addressed to the other Member States concerned;

b) during this time, the competent authority of the reference Member State may request (once) supplementary information to that already submitted;

c) if, within 30 days following the receipt of the draft decision and the succinct assessment report, no objection has been raised, the other Member States concerned accept this draft decision, inform the reference Member State to this effect, and grant the renewal of the marketing authorisation;

d) in cases where mutual recognition of the draft decision by one or more Member States is not possible i.e. there are serious grounds for supposing that the authorisation of the veterinary medicinal product concerned may present a risk to aniaml or human health or the environment, or if the draft decision of the reference Member State is unfavourable on the same grounds, a scientific evaluation of the matter would be undertaken by the CVMP (see Chapter III).

CHAPTER III
COMMUNITY REFERRAL

1. LEGAL BASIS

An authorisation to place a veterinary medicinal product on the market in one Member State ought in principle to be recognised by the competent authorities of the other Member States unless there are serious grounds for supposing that the authorisation of the veterinary medicinal product concerned may present a risk to human or animal health or the environment. In the event of a disagreement between Member States about the quality, the safety or the efficacy of a veterinary medicinal product, a scientific evaluation of the matter should be undertaken by the Committees attached to the European Agency for the Evaluation of Medicinal Products, leading to a single decision on the area of disagreement, binding on the Member States concerned. This decision should be adopted by a rapid procedure ensuring close co-operation between the Commission and the Member States.

2. SCOPE

The instances where a disagreement could arise are set out in Directive 81/851/EEC as amended and include referrals under either Articles 8 (suspension of examination),8a (obligatory mutual recognition), 18 (risk to health), 19 (divergent decisions), 20 (Community interest) or 23 (variation), 23a (protection of public health), 23b (previous concertation procedures) or 29h (pharmacovigilance).

3. MEMBER STATE LIAISON ON POTENTIAL RISK(S) TO HUMAN OR ANIMAL HEALTH OR THE ENVIRONMENT

Save in the exceptional case provided for in Article 18(1) of Directive 81/851/EEC as amended, each Member State shall recognise the marketing authorisation granted by the first Member State within 90 days of receipt of the application and the assessment report. It shall inform the Member State which granted the initial authorisation, the other Member States concerned by the application, the Committee, and the person responsible for placing the veterinary medicinal product on the market.

These articles set out the procedure to be followed where a Member State considers there are grounds for supposing that the granting of a marketing authorisation for the product concerned may present a potential "risk to human or animal health or the environment", which is defined as referring to quality, safety and efficacy. The procedure may be initiated as a consequence of a disagreement during a mutual recognition process arising from the possibilities foreseen in Articles 8, 8a and 17 of Directive 81/851/EEC as amended.

3.1 Referral to the Committee

If the concerns raised cannot be resolved within the 90 day period, the reference Member State, in consultation with the person responsible for placing the veterinary medicinal product

on the market, may refer the matter to the Committee for the application of the procedure of Article 21 of Directive 81/851/EEC as amended (even before the end of the 90 days).

In these circumstances, the concerned Member States shall provide the Committee with a detailed statement of the matters on which they have been unable to reach agreement and the reasons for their disagreement. The person responsible for placing the veterinary medicinal product on the market shall be provided with a copy of this information.

As soon as the person responsible for placing the veterinary medicinal product on the market is notified of the reference to the relevant Committee, a copy of the application should accordingly be sent to the Committee at the EMEA. This copy may be consulted at any time by any Member of the Committee. The person responsible for placing the veterinary medicinal product on the market should also certify (usually in the covering letter accompanying the application) that;

- the dossier is identical (including any approved variations) to that accepted by the reference Member State, or to identify any additions,
- the SPC is identical, and
- the dossier and SPC as submitted are identical in all concerned Member States.

4. ARTICLE 19 REFERRALS

Article 19 of Directive 81/851/EEC as amended provides that where divergent decisions have been adopted concerning a veterinary medicinal product which has been the subject of several applications for marketing authorisation in the Member States in accordance with Articles 5 and 5a of Directive 81/851/EEC as amended, the matter may be referred to the Committees for application of the procedure as laid down in Article 21 of Directive 81/851/EEC as amended. The reference may be made by either one or more of the concerned Member States, the Commission or the person responsible for placing the veterinary medicinal product on the market. In invoking Article 19, whoever makes the reference shall clearly state the reasons for invoking the procedure and identify the question(s) referred to the Committee for consideration.

4.1 Objective and scope

The free movement of veterinary medicinal products in the Community may be hindered by national decisions which, though based on the same dossier, are divergent. Article 19 provide a mechanism for the resolution of divergence. However, priority should be given to the elimination of divergences liable to have the greatest effect on the functioning of the single market.

Article 19 as amended may be invoked when divergence regarding current authorisation status of a particular veterinary medicinal product is known to exist at national level within the EC when the decisions were made on identical dossiers and the relevant applications were submitted in accordance with Articles 5 and 5a of Directive 81/851/EEC as amended.

With regard to authorisations granted before 1/1/95, Article 52 of Directive 81/851/EEC as amended required the provisions of the Directive to be applied progressively to veterinary medicinal products placed on the market by virtue of previous provisions within 15 years of the date of its notification, i.e. by October 1991. The only group of products where the review

period is not yet closed is veterinary immunologicals, where Directive 90/677/EEC as amended requires completion by 31 March 1998.

Given that only a small percentage of applications have been harmonised through the Community multi-state or concertation procedures, it is likely that there will be some divergence between existing national decisions. It would appear to be in keeping with the spirit of the legislation and in the interests of animal health and the continuity of supply of veterinary medicinal products to refer cases where significant divergences exist, e.g.

- where one Member State authorises and another refuses the same veterinary medicinal product;
- where the same veterinary medicinal product has been authorized in two or more Member States but the authorisations, particularly the indications, differ significantly.

As the principle of mutual recognition is reinforced by the legislative amendments, the likelihood of divergence after 1/1/95 therefore diminishes:-

- from 1/1/95, applications under Article 8 of Directive 81/851/EEC as amended would be mutually recognised or, in exceptional circumstances, would result in binding arbitration;
- from 1/1/95, applications under Article 17.3 of Directive 81/851/EEC as amended would be mutually recognised or, in exceptional circumstances, would result in binding arbitration;
- from 1/1/98, applications under Article 8a of Directive 81/851/EEC as amended would be mutually recognised or, in exceptional circumstances, would result in binding arbitration.

Nonetheless, divergence may still arise after 1/1/95 during the transition period, for example:

- in the case of parallel applications for the same veterinary medicinal product, submitted in two or more Member States using purely national procedures;
- where a negative decision in one or more Member State(s) is followed by a positive decision on a subsequent application in another Member State.

Referral may also be appropriate where a veterinary medicinal product, with a current marketing authorisation in some or all Member States, is suspended or withdrawn on the basis of new data on quality, safety or efficacy in some but not all of the concerned Member States.

Article 19 could be used in these circumstances.

4.2 Procedure

4.2.1 Discussion with the Member State

In advance of making a referral under these Articles, it is recommended that informal discussions take place between the person responsible for placing the product on the market and the concerned Member States. Subsequent developments or the availability of additional information may have led to the divergent decisions, and such informal discussions may obviate the need for a referral.

4.2.2 Referral

In invoking Article 19, the Member State, the person responsible for placing the product on the market, or the Commission shall clearly state the reasons for invoking the procedure and identify the question(s) referred to the Committee for consideration. Confirmation should be provided that the dossiers submitted as applications for marketing authorisation, or for consideration of suspension or withdrawal, are identical in the Member States concerned. Where appropriate, the other relevant parties, i.e. the other Member States, the Commission and the applicant shall also be informed.

In those cases where the referral comes from a concerned Member State, the reasons must be accompanied by an appropriately updated assessment report, which must include all available information relating to the matter in question.

In the case of referrals from a person responsible for placing the veterinary medicinal product on the market, the reasons must be accompanied by expert reports on quality, safety and efficacy which take account of current regulations and which have been updated to include data supporting the reasons for referral.

4.2.3 Time-frame

For referrals in accordance with Article 19, the Committee considers the matter and issues an opinion within 90 days of the date of referral. This period may be extended by a further 90 days. In case of urgency, on a proposal from its Chairman, the Committee may agree to impose a shorter deadline.

5. ARTICLE 20 REFERRALS

5.1 Legal basis

Article 20 of Directive 81/851/EEC as amended provides that where the interests of the Community are involved, the Member States, the Commission or an applicant or holder of the marketing authorisation may refer the matter to the Committee for application of the procedure as laid down in Article 21 of Directive 81/851/EEC as amended, before reaching a decision upon a request for a marketing authorisation, or the suspension, withdrawal or variation of an existing marketing authorisation.

5.2 Objective and scope

Where the interests of the Community are involved, a procedure for arriving at a rapid opinion has been foreseen. The amendment introduced by Directive 93/40/EEC provides for referrals in cases relating to applications, suspensions or withdrawals, including variations of Community or national authorisations. In addition, referrals may be made by Member States, the Commission, or the marketing authorisation holder or applicant.

It is important that this Article is not interpreted as setting up an alternative procedure for new applications - preference must always be given to either the centralised or mutual recognition procedures. Equally, a referral must be in the interests of the Community and therefore must be determined on a case by case basis.

Where the interests of the Community are involved, a referral could be made in relation to:-

- a request for marketing authorisation of a product which appears to be of the highest importance from the point of view of protection of human or animal health or the environment but which is **not** eligible for the centralised procedure (reference under Article 20 would not be appropriate in respect of products which are eligible for Part B);
- a proposal for suspension or withdrawal of an authorisation, in the light of new data relating to quality, safety or efficacy;
- a variation to the terms of the authorisation appearing necessary, especially in the light of any new pharmacovigilance information available.
- a proposal for granting or refusing a variation to the terms of a marketing authorisation.

5.3 Procedure

The person responsible for invoking Article 20 (Member States, the person responsible for placing the product on the market, the Commission) shall clearly state the question which is referred to the Committee for consideration and shall inform the other concerned parties.

The Member States and the person responsible for placing the product on the market shall forward to the Committee all available information relating to the matter in question.

In those cases where the referral comes from a concerned Member State, the reasons must be accompanied by an updated assessment report which includes all available information relating to the matter in question.

In the case of referrals from a marketing authorisation holder, the reasons must be accompanied by expert reports on quality, safety and efficacy which take account of current regulations and which have been updated to include data supporting the reasons for referral. In addition, the MA holder must ensure that all the concerned Member States have the updated or additional information available to them.

5.4 Time-frame

Article 21 of Directive 81/851/EEC requires the Committee to consider the matter and issue a reasoned opinion within 90 days of the date of referral. This period may be extended by a further 90 days. In case of urgency, on a proposal from its Chairman, the Committee may agree to impose a shorter deadline.

6. VARIATIONS AND SUSPENSIONS BY AUTHORITIES

The amendments to Directive 81/851/EEC provide that where a Member State considers that variation of the terms of a marketing authorisation which has been authorised by mutual recognition (or subsequent arbitration), or its suspension or withdrawal, is necessary for the protection of human or animal health or the environment, it **must** refer the matter to the Committee for application of the procedure as laid down in Article 21. Article 21 of Directive 81/851/EEC as amended require the Committee to consider the matter and issue a reasoned opinion within 90 days of the date of referral.

Article 42h of Directive 81/851/EEC as amended provides that where as a result of the evaluation of adverse reaction reports a Member State considers that a marketing authorisation should be varied, suspended or withdrawn, it must inform the Agency and the person responsible for placing the veterinary medicinal product on the market. In case of urgency, the Member State concerned may suspend the marketing authorisation. If it does so, it must inform the Agency at the latest on the following working day. In cases where the Community interest are involved, this would be dealt with in accordance with Article 20 of Directive 81/851/EEC as amended.

In exceptional cases where urgent action is essential to protect human or animal health or the environment, a Member State may, until a definitive decision is adopted, suspend the marketing and the use of the veterinary medicinal product concerned on its territory. The Member State must inform the Commission and the other Member States no later than the following working day of the reasons for its action.

7. THE ARBITRATION PROCEDURE

7.1 Appointment of a Rapporteur to consider risks to human or animal health or the environment.

To assist in its review of the outstanding grounds for supposing that serious risks to human or animal health or the environment may remain, the Committee will appoint a rapporteur from one of its members. The choice of rapporteur will depend on the product and the nature of the human or animal health or the environmental objections raised. Whilst it may be convenient to choose a Committee member from the reference Member State, there may be cases where a different rapporteur may be more appropriate. The Agency will notify the person responsible for placing the veterinary medicinal product on the market of the identity of the rapporteur. Where necessary, additional experts may be appointed to assist the rapporteur and to advise on specific defined questions.

7.2 Timetable for the arbitration

The timings shown are indicative. The timetable will be reviewed by the Committee rapporteur in conjunction with the person responsible for placing the veterinary medicinal product on the market.

Referral to the Committee	**Timing**[2]
Committee discussion on: - question which has been referred (e.g. human or animal health or the environment objections raised by concerned Member States; divergent decisions; interests of the Community) - views of the reference Member State, concerned Member States, the person responsible for placing the veterinary medicinal product on the market, the Commission - appointment of Committee rapporteur - appointment of individual experts, if needed - request for comments upon the question referred (human or animal health or the environment) from the person responsible for placing the veterinary medicinal product on the market	Day 1
Committee stops the clock while the person responsible for placing the veterinary medicinal product on the market produces comments in writing (60 days will normally be allowed for written comments, but the Committee may extend this period either on their own initiative or at the request of the person responsible for placing the veterinary medicinal product on the market)	Day 2
Person responsible for placing the veterinary medicinal product on the market submits comments to all members of the Committee in writing Clock restarts when all documentation is received, timetable is distributed	Day 3
Rapporteur prepares a report with conclusions on the written comments of the person responsible for placing the veterinary medicinal product on the market upon the objections relating to human or animal health or the environment	by Day 45
Comment from the Committee members on the conclusions of the assessment report to the rapporteur	by Day 60
Rapporteur liaises with the person responsible for placing the veterinary medicinal product on the market to highlight remaining issues, if any, and to give guidance on the oral explanation in the Committee, if necessary	
Oral explanation before Committee and Committee opinion on the points of arbitration	Day 90

[2] *When reference is made to the procedure described in this Article, the Committee shall consider the matter concerned and issue a reasoned opinion within 90 days of the date on which the matter was referred to it.*
However, in cases submitted to the Committee in accordance with Articles 19 and 20, this period may be extended by 90 days.
In case of urgency, on a proposal from its Chairman, the Committee may agree to impose a shorter deadline.

7.3 Committee Assessment Report.

The Committee rapporteur will prepare a Report of the Assessment on the written information. A copy of the report will be sent to the person responsible for placing the veterinary medicinal product on the market and the Committee members. The objective of this report is to provide an assessment on the issues relating to human or animal health or the environment which remained in relation to the product in the light of the explanation of the person responsible for placing the veterinary medicinal product on the market.

7.4 Oral explanation

Oral explanations are part of the formal process and not to be confused with other informal meetings between persons responsible for placing the veterinary medicinal product on the markets, rapporteurs, other Member States, etc.

Practical arrangements for oral explanations will be organised by the Agency.

In order to maximise the benefit of an oral explanation, it is important that persons responsible for placing the veterinary medicinal product on the market and preparing to attend a Committee meeting for the purpose of an oral explanation bear in mind that its aim is to allow clarification of outstanding issues. They should remember:

a) that the oral proceedings of the Committee are multi-lingual. Persons attending should notify the Agency in good time of the language(s) in which they intend to express themselves so that, if necessary, arrangements for interpretation can be ensured. Although there is normally simultaneous interpretation in most Community languages, arguments of a very technical or scientific nature are usually better expressed in writing.

b) to liaise with the rapporteur regarding the content of any written documents, slides and overheads to be used. 50 copies of any visual aid material, including paper copies of overhead projector slides/overheads, should also be brought to the meeting for distribution immediately beforehand.

c) for practical purposes, to limit the delegation to a small number. Depending on the issues raised, it would normally be appropriate for between one and four persons per company to appear on behalf of the person responsible for placing the veterinary medicinal product on the market, with a maximum of eight.

7.5 Committee Opinion

After consideration of the written representation and oral explanation, the Committee reaches an opinion on the points upon which were referred to it.

Where the opinion of the Committee is that:

- the application does not satisfy the criteria for authorisation, or
- the SPC should be amended , or
- the authorisation should be granted subject to conditions with regard to the safe and effective use of the veterinary medicinal product including pharmacovigilance, or
- the authorisation in the reference Member State and any other EC Member States in which the product is authorised should be suspended, varied or withdrawn,

the Agency will forthwith inform the person responsible for placing the veterinary medicinal product on the market.

In the event of an opinion in favour of granting or maintaining an authorisation to place the veterinary medicinal product concerned on the market, the following documents shall be annexed to the opinion:

a) a draft summary of the product characteristics, as referred to in Article 5a of Directive 81/851/EEC as amended ;

b) any conditions affecting the authorisation

Within 30 days of adoption of the opinion, it is sent by the Agency to the Member States, the Commission and the person responsible for placing the veterinary medicinal product on the market. Within 15 days of receipt of the opinion, the person responsible for placing the veterinary medicinal product on the market may notify the Agency of the intention to appeal. In that case detailed written grounds for appeal shall be forwarded to the Agency within 60 days of the opinion. The Committee shall consider whether its opinion should be revised.

7.6 Appeal Process

Within 60 days, the Committee will reach a decision whether its opinion should be revised. In order to do so, it may appoint one of its members to act as rapporteur (generally a different member than that which had already acted as rapporteur for this veterinary medicinal product).

The rapporteur is responsible for making an assessment, within 30 days of receipt of the documentation, of the grounds for appeal. The assessment report would consist of a summary of the appeal, a discussion of each of the grounds for appeal and a conclusion in which is stated which of the issues can be considered as resolved and which will still remain.

This assessment report with a proposal for revision of the original opinion, if necessary, annexed to it, is prepared.

The Committee will consider the report together with the original opinion and issue its decision within 60 days of receipt of the grounds for appeal. The company concerned may be afforded the opportunity to make an oral explanation.

7.7 Binding decision

Where the provisions of Article 13 have been followed, and the opinion of the Committee is forwarded to the Commission for the decision making process foreseen in Article 42k of Directive 81/851/EEC as amended, this leads to a Decision which is legally binding on all Member States. Thus, where a Member State has previously authorised the veterinary medicinal product, it may be necessary to change the marketing authorisation, within 30 days, in keeping with the decision.

CHAPTER IV

CENTRALISED PROCEDURE

1. LEGAL BASIS AND PURPOSE

EC Regulation No. 2309/93 introduced the centralised procedure, a procedure for which there is a single application, single evaluation and a single authorisation for a medicinal product leading to direct access to the single market of the Community.

Regulation No. 2309/93 responded to the need to protect public health within the Community whilst at the same time allowing rapid access to the single market for important new medicinal products. The regulation built upon the experience of the concertation procedure which had been set up by Directive 87/22/EEC in order to ensure the smooth functioning of the internal market in the pharmaceutical sector, and relied upon the fundamental principle that the authorisation of medicinal products should be based on objective scientific criteria of quality, the safety and the efficacy of the medicinal product concerned.

A marketing authorisation granted following the centralised procedure is valid for the entire Community market. A Community authorisation applies to all Member States which means the medicinal product may be put on the market in all Member States. Whilst a pharmaceutical company is not required to sell a medicinal product in all parts of the territory of the Community, a marketing authorisation holder cannot prevent a medicinal product which has been authorized centrally from being sold throughout the Community.

2. SCOPE

Applications which fall within the scope of Regulation (EEC) No. 2309/93 are set out in the Annex to that regulation. Applications for medicinal products listed in Part A of the annex are required to use the centralised procedure, while applications for medicinal product listed in Part B of the annex may, at the request of the applicant, use the centralised procedure.

At set out in Chapter I, it is important from an administrative point of view that a consistent regulatory strategy is maintained, both for the applicant and for the competent authority. Therefore, whilst not obligatory, it is nonetheless recommended that for applications using Part B of the Annex of Regulation (EEC) No. 2309/93, the optionality provided for in the legislation should not be interpreted as a mechanism to partition the market. Thus for abridged applications (e.g. informed consent and extensions) the option to use either the centralised route or mutual recognition route is available. Where such abridged applications use the mutual recognition procedure, both the Member States and the Commission must take up their responsibilities regarding the maintenance of a harmonised market, including as necessary, availing of references in accordance with article 12 of Directive 75/319/EEC as amended in cases of Community interest.

In accordance with Articles 13.4 and 35.3 of Regulation (EEC) No. 2309/93, medicinal products for human use and veterinary medicinal products which have been authorised by the Community shall benefit from the ten year period of protection referred to in point 8 of the second paragraph of Article 4 of Directive 65/65/EEC and in point 10 of the third paragraph of Article 5 of Directive 81/851/EEC respectively.

2.1 Part A - medicinal products derived from biotechnology

Persons wishing to obtain a marketing authorisation for a medicinal product developed by means of one of the following biotechnological processes:

i) recombinant DNA technology,

ii) controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells,

iii)hybridoma and monoclonal antibody methods

must submit the application to the European Agency for the Evaluation of Medicinal Products and the application will be processed in the centralised procedure.

This requirement also applies to veterinary medicinal products, including those not derived from biotechnology, intended primarily for use as performance enhancers in order to promote the growth of treated animals or to increase yields from treated animals.

Unlike in the concertation procedure (Directive 87/22/EEC) there is no provision for an application for a Part A medicinal product to only one Member State being exempted from the scope of the centralised procedure.

2.2 Part B - innovatory medicinal products

In addition, innovatory medicinal products with novel characteristics as defined in Part B of the Annex to Regulation No. 2309/93 may, at the request of the applicant, be accepted for consideration under the centralised procedure. In addition applications for medicinal products containing a new active substance may also use the centralised procedure.

The following categories of medicinal products for human or veterinary use are eligible for Part B status:-

"Medicinal products developed by other biotechnological processes which, in the opinion of the Agency, constitute a significant innovation.

Medicinal products administered by means of new delivery systems which, in the opinion of the Agency, constitute a significant innovation.

Medicinal products presented for an entirely new indication which, in the opinion of the agency, is of significant therapeutic interest.

Medicinal products based on radio-isotopes which, in the opinion of the Agency, are of significant therapeutic interest.

New medicinal products derived from human blood or human plasma.

Medicinal products the manufacture of which employs processes which, in the opinion of the Agency, demonstrate a significant technical advance such as two-dimensional electrophoresis under micro-gravity.

Medicinal products intended for administration to human beings, containing a new active substance which, on the date of entry into force of this Regulation, was not authorized by any Member State for use in a medicinal product intended for human use.

Veterinary medicinal products intended for use in food-producing animals containing a new active substance which, on the date of entry into force of this Regulation, was not authorized by any Member State for use in food-producing animals".
(extract from Annex to Regulation No. 2309/93)

2.3 Variations to the terms of a marketing authorisation

Regulation No. XX/95 sets out the procedure for varying the terms of the marketing authorisation granted by the Community.

The procedure for the examination of a variation is identical whether the product is Part A or B.

2.4 Renewal of marketing authorisations

According to Article 15.1 of Council Directive 81/851/EEC, a marketing authorisation for a veterinary medicinal product shall be valid for five years and be renewable for five-year periods upon application by the holder at least three months before expiry.

For a veterinary medicinal product which has been authorized by the Community, the application for renewal of the marketing authorisation should be submitted to the Agency at least three months before the expiry of the marketing authorisation.

3. PRE-SUBMISSION

3.1 Advice to companies

According to Article 51 (j) of Regulation (EEC) N° 2309/93, it is the task of the Agency within its Committees "where necessary, to advise companies on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products".

The new CVMP has been constituted early in 1995. The Committee will wish to consider the appropriate mechanism for complying with article 51(j) of the Regulation. The following procedure is a provisional one designed mainly to deal with major issues of scientific principle concerned with the development of a new veterinary medicinal product.

This provisional procedure, the scope and timing of advice to be given to companies will be revised in the light of experience

3.1.1 Necessity for advice

Normally, advice is prepared in the form of guidelines which are published by the European Commission in 'The Rules governing medicinal products in the European Union.' A series of guidelines has already been published in Volume VII.

Advice of the Agency, within its Committees, on the conduct of tests and trials to demonstrate the quality, safety and efficacy of medicinal products may be requested for products eligible for authorisation by the centralised procedure. In the case of a medicinal product referred to in Part B of the Annex to Regulation 2309/93, its suitability for authorisation via the centralised procedure must be confirmed, in principle, before advice can be given.

Advice will only be given in those circumstances where Pharmacopoeia monographs or guidelines, especially those adopted by the CVMP and CPMP and published, do not already address the point of concern or do not provide sufficient guidance.

The ultimate decision as to what advice, if any, will be given rests with the Agency.

3.1.2 Scope of advice

Applicant companies seeking advice under Article 51(j) must note that any advice given is not and will not be binding on the Agency with regard to the eventual application for marketing authorisation of the concerned product.

Advice will be given in good faith but circumstances could change especially in the case of early advice or subsequent scientific developments. In some cases, e.g. as a result of scientific developments, an alternative approach to that advised may be appropriate. However where companies choose not to apply the advice, an explanation should be provided in the appropriate part of the dossier.

The applicant should take into account that the scope of advice offered shall be general rather than specific (e.g. the already published guidelines on the conduct of various tests and trials may serve as examples for the general scope of advice). Questions should be limited to general problems of the tests or trials (e.g. it is not possible to give advice on the number of test animals or on statistical analysis). However, on occasions, detailed advice may be appropriate.

3.1.3 Consultation procedure

If a company considering making an application for marketing authorisation requires technical advice, it shall bring forward a written request to the secretariat of the Agency. The request must identify clearly (in a maximum of 4 pages) the questions/issues to be addressed and the reasons why advice is being requested from the Committee, particularly why existing publications or guidelines cannot be used.

Each request will be considered by the Agency within its Committees as to the true necessity for such advice on a case by case basis and if appropriate the relevant Committee(s) may decide to refuse to give advice.

The procedure to be followed will be determined on a case by case basis depending on the nature of the request. Usually, the Committee concerned will appoint one of its members to co-ordinate advice to industry.

If necessary, the co-ordinator and the company shall undertake appropriate consultations which may be oral or written but shall in any event be documented.

After this, the following steps could apply :

i) The company shall prepare a report summarising the discussions;

ii) The report shall be discussed by the co-ordinator and the company to reach agreement;

iii) The co-ordinator shall inform the Committee;

iv) The members of the Committee may provide written comments to the co-ordinator;

v) The co-ordinator shall prepare a response incorporating advice to the company taking into account all comments received;

vi) After any necessary discussion, the Committee shall recommend the advice to be given which shall be transmitted to the company by the Agency.

Furthermore the Committee shall consider whether or not the case would lead to

a) the amendment of guidelines;

b) the preparation of new guidelines;

c) and/or the dissemination of information, for example, through a press release.

Where considered appropriate, e.g. in cases of minor concern, the Committee may decide on a different approach to be followed. The procedure followed and the advice given shall be documented.

3.2 Verification of Part B status:

When an applicant considers that a medicinal product is a significant innovation or of significant therapeutic interest or a significant technical advance under one or more of the indents in Part B, and would therefore wish to avail of a Community procedure for access to the single market, contact should be established with the Agency. In the case of a new active substance which, on the date of entry into force of Regulation (EEC) Nr. 2309/93, was not authorized by any Member State for use in a medicinal product, the centralised procedure may be used (see section 3.2.1 below).

In the case of very innovative treatment, companies may ask the advice of the Agency. In such cases, the acceptance, in principle, of the application falling within the scope of Part B would be a prerequisite to the process of consultation.

An application may be accepted as falling, in principle, within the scope of Part B, even before the application dossier is finalised. In such circumstances, the applicant should provide a document (2-3 pages) describing the properties of the product in which the

innovative character according to one of the above mentioned indents is especially elaborated.

The Committee is responsible for formulating the opinion of the Agency on any question relating to the admissibility of an application. In the event that the application is accepted as falling within the scope of Part B, the applicant will be advised by the Agency.

It is not essential that the application be submitted immediately.

Definition of a new active substance

A new chemical, biological or radiopharmaceutical active substance includes:

i) a chemical, biological or radiopharmaceutical substance not previously authorized as a medicinal product in the European Community;

ii) an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously authorized as a medicinal product in the European Community but differing in properties with regard to safety and efficacy from that chemical substance previously authorized;

iii) a biological substance previously authorized as a medicinal product in the European Community, but differing in molecular structure, nature of the source material or manufacturing process;

iv) a radiopharmaceutical substance which is a new radionuclide, or a ligand not previously authorised as a medicinal product in the European Community, or the coupling mechanism to link the molecule and the radionuclide has not been previously authorised in the European Community.

3.3 Inspection of the manufacturing site

3.3.1 Products manufactured in the European Economic Area

The rapporteur's assessment report will give information with regard to the suitability of the proposed manufacturer(s), including confirmation from the supervising Member States that the manufacturer of a veterinary medicinal product or the importer from a third country is able to manufacture the veterinary medicinal product concerned and/or carry out the necessary control tests in accordance with the particulars and documents supplied pursuant to Article 28 of Regulation (EEC) No. 2309/93. The procedure for the exchange of information on manufacturing authorisations (established by the ad hoc group on harmonisation of inspections) is set out in "Compilation of Community procedures on administrative collaboration and harmonisation of inspections, III/5698/94, Nov. 1994").

3.3.2 Products manufactured outside the European Economic Area

Where it is considered necessary to complete the examination of an application, the rapporteur may recommend to the Committee that the applicant submit to a specific inspection of the manufacturing site(s) of the veterinary medicinal product concerned. The inspection would be undertaken by inspectors from the Member States who possess the appropriate qualifications and experience and who may, if need be, be accompanied by a rapporteur or expert appointed by the Committee.

In the absence of a Mutual Recognition Agreement on inspection and good manufacturing practice, it is likely that a Community inspection would be systematic for applications through the centralised procedure. Thus, for veterinary medicinal products which are to be manufactured outside the EEA, the applicant should liaise with the Agency well in advance of the submission of an application in order to avoid delays due to arranging inspections or effecting required remedial measures. Where necessary, the scientific evaluation may be suspended pending receipt of the inspection report.

3.4 Liaision with the Agency

Applicants are reminded that the initial contact point in a centralised procedure is the Agency. The applicant is advised to notify the Agency of the intention to submit an application about 3 to 6 months in advance, in order that preparations and scheduling may be initiated and to ensure that the application will be complete and valid (see 'Dossier Check-in Procedure' in Chapter VII) according to current requirements.

4. SUBMISSION OF THE APPLICATION

4.1 Dossier for submission

The application is submitted to the Agency at

7 Westferry Circus,
Canary Wharf,
GB-London E14 4HB

and should be marked for the attention of NN.

When the application is made, one copy is forwarded to the Agency for the two-weeks validation period. At its next meeting, the CVMP will appoint or confirm the rapporteur and the co-rapporteur, who should then receive two copies each. At this stage the CVMP also determines if any of its members should receive an extra copy.

Thirty-four copies of Part I should be prepared. They are to be distributed as follows: four copies are to be forwarded to the EMEA at the time the full dossier is submitted. One copy should be forwarded to each member of the CVMP.

In the case of a veterinary medicinal product containing or consisting of genetically modified organisms within the meaning of Article 2.1 and 2.2 of Directive 90/220/EEC, the application must also be accompanied by:

i) a copy of any written consent or consents of the competent authorities to the deliberate release into the environment of the genetically modified organisms for research and development purposes where provided for by Part B of Directive 90/220/EEC,

ii) the complete technical dossier supplying the information requested in Annexes II and III to Directive 90/220/EEC and the environmental risk assessment resulting

from this information; the results of any investigations performed for the purposes of research or development.

Applicants are reminded that Part IB (drafts of the summary of product characteristics, package insert and labels) must be submitted in all the languages of the Community.

The application fee should be included with the submission i.e. bank transfer. Applications will not be processed until the full fee has been paid.

4.2 Check-in of the application

The application is checked in by the secretariat of the Agency within 10 working days of receipt, using the check-in procedure.

Receipt of a valid application is notified to the applicant by the secretariat. Any problems are notified immediately in writing (by telefax) directly to the applicant and in the event that the deficiency cannot be rectified within 1 month, the dossier will be returned to the applicant, and a proportion of the fee will be retained to cover administration charges.

5. PROCEDURE FOR SCIENTIFIC EVALUATION

5.1 Selection of rapporteur/co-rapporteur

The Committee appoints one of its members to act as rapporteur for the co-ordination of the evaluation of an application, taking into consideration any proposal from the applicant for the choice of a rapporteur. Thus in the covering letter which accompanies the dossier, the applicant should set out their proposal for rapporteur, if any.

The Committee will select the rapporteur from amongst its members in such a way as to ensure that there is appropriate co-ordination between the tasks of the Agency and the work of competent national authorities, including the consultative bodies concerned with the marketing authorisation. Selection of the rapporteur will be by consensus. If such a consensus cannot be reached, the selection will be the position of the majority of members.

The Committee may appoint a second member to act as co-rapporteur. Appointment of a co-rapporteur will not be systematic. However, in cases where a wide-ranging scientific debate would be constructive, a co-rapporteur could be appointed. The role of the co-rapporteur would be determined by the Committee on a case by case basis.

The Committee shall ensure that all its members undertake the role of rapporteur or co-rapporteur.

5.2 Selection of the evaluation team

Member States, in accordance with article 51 of Regulation (EEC) No. 2309/93, have transmitted lists of experts with proven experience in the assessment of medicinal products. This list is updated as necessary.

In forming the evaluation team, the rapporteur will nominate experts from this list, in consultation with the Committee (a procedure may be elaborated by the new Committees).

The members of the Committees and the experts responsible for evaluating medicinal products rely on the scientific assessment and resources available to the national competent authorities. However, the assessment report is prepared for and on behalf of the Community.

5.3 Timetable for the evaluation

The timings shown are indicative. The timetable proposed by the rapporteur will be reviewed by the Agency in conjunction with the Committee and the applicant.

Note : The new Committees may wish to elaborate procedures for the preparation of the timetable and to give further advice on aspects relating to the scientific evaluation process. In addition, the Committees may, in the light of experience, wish to improve the procedure in this context.

Scientific Evaluation	Timing
Committee receives the valid application, a rapporteur (taking into consideration any proposal from the applicant for the choice of a rapporteur) and as appropriate a co-rapporteur, is nominated along with the experts in the evaluation team; The secretariat liaises with the applicant, informing them of the rapporteur (and co-rapporteur) and timetable which has been prepared.	Day 1
Rapporteur (and co-rapporteur, as appropriate) circulate their preliminary assessment reports to the Committee	Day 90
Committee considers preliminary assessment report(s) and establishes those issues which the applicant is invited to clarify and the clock is stopped	Day 120
Applicant submits a written response to the Agency Clock restarts when a response to all parts of the dossier is received	Day 120
Rapporteur(/co-rapporteur) prepares a report with conclusions on the written response of the applicant and circulates to members and the applicant	Day 150
The need for an oral explanation with the Committee is discussed with the rapporteur, which is then is arranged by the secretariat if necessary (clock may be stopped to allow the applicant to prepare the oral explanation)	Day 180 approx.
The Committee members conclude the evaluation and adopt the opinion	Day 210

5.4 Discussion with the rapporteur

Once the rapporteur has been appointed by the Committee, the name of the rapporteur and the timetable will be sent to the applicant by the Agency. Liaison between the rapporteur and the applicant should be initiated by the rapporteur.

The rapporteur is responsible for liaison with the applicant should any clarification of the dossier be required.

When the Committee has considered the preliminary assessment report(s) and established those issues which the applicant is invited to clarify, these texts will be made available to the applicant by the Agency. All preliminary reports or other documents in advance of this stage are considered internal papers of the Committee and cannot be taken as representing the position of the Committee.

The time limit laid down in Article 28 of Regulation (EEC) No. 2309/93 shall be suspended until such time as the supplementary information requested has been provided.

5.5 Supplementary information

The applicant may prepare supplementary information to the preliminary assessment report on those issues raised for clarification/completion. The issues, including those quality issues raised in an inspection report, should be presented in the order of the sequence for the dossier with their responses. Where appropriate, a revised text of the proposed SPC, label(s) and package inserts should also be included in the supplementary information.

The response should include:

i) the name, trade name and composition of the veterinary medicinal product,

ii) the name and address of the applicant

iii) centralised procedure reference number (and amendment/variation if relevant).

iv) the text of the proposed SPC and package insert, revised appropriately in the light of the list of issues raised by the Committee.

Each answer should start on a new page with a repetition of the particular point/points from the list of issues.

The applicant should send the supplementary information in accordance with the agreed timetable to the Agency, (see Chapter VII for the numbers of copies required). An oral explanation may be requested by the applicant at the same time as the supplementary information is submitted.

In the likelihood of a prolonged delay in preparation of the supplementary information, the applicant should notify the Agency, giving an indication of the time needed to finalise the supplementary information. It is not considered that a delay of longer than six months should normally be needed. In such an event, liaison with the Agency is essential.

The applicant is advised to liaise with the rapporteur regarding the strategy for the response and in particular, the adaptation of the draft SPC. The applicant may consult with and/or

meet the rapporteur before the Committee meeting to be briefed on outstanding points and strategy for the opinion/oral explanation. If an oral explanation was originally requested, the actual need for one is reviewed in discussion between the rapporteur and applicant.

5.6 The oral explanation

In addition to written supplementary information on issues raised for clarification, the applicant may also avail of an oral explanation with the Committee. The time limit set out in article for the 28of the Regulation (EEC) No. 2309/93 shall be suspended for the time allowed to the applicant to prepare an oral explanation.

In order to maximise the benefit of an oral explanation, it is important that applicants preparing for and attending oral explanations bear in mind that they are held to allow clarification of outstanding issues. Thus the applicant should remember:

i) That the oral proceedings of the Committee are multi-lingual. Persons attending such oral explanations should notify the Committee secretariat in good time of the language(s) in which they propose to express themselves so that, if necessary, arrangements for interpretation can be ensured. Although simultaneous interpretation into most Community languages is normally available, arguments of a technical or scientific nature are better expressed in writing.

ii) Applicants should liaise with the rapporteur regarding the content of written documents/slides/overheads which are to be used in conjunction with an oral explanation. 50 copies of any visual aid material, including paper copies of projector slides/overheads, should also be brought to the meeting, for distribution just prior to the oral explanation.

iii) Depending on the issues raised in the reasoned objections, it would normally be appropriate for between one and four persons per company to appear on behalf of the applicant. However, due to limited space in meeting rooms, a maximum of 8 persons can be accommodated.

There are currently no formal rules for the conduct of oral proceedings. The new Committees may wish to develop appropriate guidance in due course.

6. THE COMMITTEE OPINION

The members of the Committee discuss the application in the light of the recommendation of the rapporteur and further evidence/argument presented at the oral explanation.

An opinion is prepared, which may be favourable or unfavourable. Where a scientific consensus cannot be obtained, the majority position is given as the opinion, with divergent positions and the reasons for such positions being included at the request of the members concerned.

Within 30 days of its adoption, the Agency shall forward the opinion of the Committee to the Commission, the Member States and the applicant together with a report describing the assessment of the medicinal product by the Committee and stating the reasons for its conclusions.

6.1 Favourable opinion

In the event of an opinion in favour of granting the relevant authorisation to place the veterinary medicinal product concerned on the market, the following documents are annexed to the opinion:

i) a draft summary of the product characteristics, as referred to in Article 5a of Directive 81/851/EEC;

ii) details of any conditions or restrictions which should be imposed on the supply or use of the medicinal product concerned;

iii) the draft text of the labelling and package insert proposed by the applicant in all EC languages;

iv) the assessment report.

Within 15 days of receipt of the opinion, and if the applicant accepts the amendments and/or conditions imposed, he may inform the Agency of his decision not to appeal. The Agency would thus forward the opinion (and the required annexes) within 30 days of its adoption, to the Commission, the Member States and the applicant together with a report describing the assessment of the medicinal product by the Committee and stating the reasons for its conclusions.

6.2 Unfavourable opinion

The Agency immediately informs the applicant when the opinion of the Committee is that:

i) the application does not satisfy the criteria for authorisation set out in Regulation (EEC) No. 2309/93, or

ii) the summary of the product characteristics proposed by the applicant should be amended, or

iii) the labelling or package insert of the product is not in compliance with Chapter VII of Directive 81/851/EEC as amended

iv) the authorisation should be granted subject to the conditions provided for in Article 35.2 of Directive 81/851/EEC as amended.

6.3 Appeal

Within 15 days of receipt of the opinion, the applicant may provide written notice to the Agency that he wishes to appeal. In that case he shall forward the detailed grounds for his appeal to the Agency within 60 days of receipt of the opinion.

Within 60 days of the receipt of the grounds for appeal, the Committee shall consider whether its opinion should be revised, and the conclusions reached on the appeal shall be annexed to the assessment report.

When considering appeals from applicants, the Committee would normally have recourse to additional experts who have not participated in the initial consideration of the dossier. To maintain the scientific credibility of the final opinion, the choice of these experts would be based upon their qualifications and experience, taking into due consideration the issues under appeal.

An oral explanation is not provided for in Regulation (EEC) No. 2309/93. Given that the time period is short, the possibility of an oral explanation during an appeal will be reserved to those cases where the Committee considers that it would contribute to the discussions, and would be at the invitation of the Agency.

7. VARIATIONS

Throughout the life of a veterinary medicinal product, the holder of the authorisation is responsible for the product which circulates in the marketplace and is also required to take into account technical and scientific progress, and to make any amendments that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods.

Marketing authorisation holders may, in addition, wish to alter/improve the product or to introduce an additional safeguard during the period of five years.

Such changes or 'variations' may involve administrative and/or more substantial changes, and the procedures for the approval of such changes, without jeopardising public health, have been set out in Regulation (EEC) No. XX/95.

The term variation is defined in Regulation (EEC) No. XX/95: "variation to the terms of a marketing authorisation" as : *an amendment to the contents of the documents referred to in Article 6(1) and (2) or Article 28(1) and (2) of Council Regulation (EEC) No 2309/93 such as they existed at the moment the decision on the marketing authorisation has been adopted in accordance with Article 10 or Article 32 of that Regulation or after approval of any previous variations, except where a new application for a marketing authorisation must be presented pursuant to Annex II of this Regulation.*

The application for the variation is submitted to the Agency, accompanied by the appropriate fee and documentation.

7.1 Urgent Safety Restriction

An urgent safety restriction is defined in Article 2.2 of Regulation (EEC) No. XX/94 as : "*An interim change to product information by the marketing authorisation holder restricting the indication(s), and/or dosage, and/or target species of the medicinal product; or adding a contra-indication, and/or warning due to new information having a bearing on the safe use of the product*".

The person responsible for placing the veterinary medicinal product on the market must immediately inform the Agency, the Commission and the Member States of any new information which might influence the evaluation of the benefits and risks of the product.

In cases of urgency, where there is a risk to public health, marketing authorisation holders may make urgent safety restrictions in accordance with Regulation XX/95. These measures

must be communicated without delay to the EMEA. If the EMEA has not raised any objections within 24 hours, the urgent safety restrictions may be introduced and the corresponding application for this variation (type II) shall be submitted without delay to the EMEA, for application of the procedures set out in Articles 6 and 7 of Regulation XX/95.

7.2 Type I variations

A "minor variation" (type I) means a variation as defined in Article 2 and listed in Annex I to Regulation (EEC) No. XX/95, provided the conditions for such variation laid down in the Annex are met.

The procedure and documentation required for a type I variation are set out in the regulation. As an illustrative guide, the following procedure would generally be followed.

a) initial application acceptable

Application submitted to the European Agency ↓ Variation assessed through a Committee procedure (which may include delegation of certain variations to the technical secretariat) ↓ Entry into the *Community Register of Medicinal Products* as appropriate and notification of the Commission (i.e. approved without the necessity for written confirmation of approval)	Day 0 ↓ ↓ ↓ ↓ ↓ Day 30

b) initial application not acceptable - marketing authorisation holder does not amend

Application submitted to the European Agency ↓ Variation assessed through a Committee procedure (which may include delegation of certain variations to the technical secretariat) ↓ If there are objective grounds against acceptance of the application, the marketing authorisation holder is sent a notification with grounds. Marketing authorisation has 30 days to amend the application taking into account the objective grounds ↓ If no responce is received, the application is deemed to have been rejected.	Day 0 ↓ ↓ ↓ ↓ Clock stopped for 30 days ↓ ↓ ↓ Day 30

c) initial application not acceptable - marketing authorisation holder does amend

<table>
<tr><td colspan="2">Application submitted to the European Agency
↓
Variation assessed through a Committee procedure (which may include delegation of certain variations to the technical secretariat)
↓
If there are objective grounds against acceptance of the application, the marketing authorisation holder is sent a notification with grounds. Marketing authorisation has 30 days to amend the application taking into account the objective grounds
↓
Amendment is submitted to the Agency
↙ ↘</td><td>Day 0
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Clock stopped for 30 days
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<tr><td>Entry into the Community Register of Medicinal Products as appropriate and notification of the Commission (i.e. approved without the necessity for written confirmation of approval)</td><td>If the amendment is not acceptable, the variation is refused, with written notification</td><td>↓
↓
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↓
Day 30</td></tr>
</table>

7.3 Type II variations

A "major variation" (type II) means a variation which cannot be deemed to be a type I variation within the meaning of Article 2 of the Regulation and which does not require a new application.

Application submitted to the European Agency ↓ Variation assessed by the Committee (generally the same rapporteur as acted for the full application). A single request for supplementary information may be made and the 'clock' could be stopped for a period of 60 days. These 60 days may be extended by the Committee (on its own initiative or at the request of the marketing authorisation holder) ↓ Assessment report circulated to the Committee ↓ Opinion of the Committee ↓ (Appeal procedure may be invoked by the marketing authorisation holder - see section 6.3) ↓ Opinion is sent by the Agency to the Commission for the normal decision-making process ↙ ↘ Decision by the Commission Refusal in writing Acceptance in writing	Day 0 ↓ ↓ ↓ ↓ ↓ ↓ Day 45 ↓ Day 60 ↓ ↓ ↓ ↓ Day 90 ↓ ↓ ↓ Day 150

8. COMMISSION DECISION

Within 30 days of receipt of the opinion from the Agency, the Commission prepares a draft of the decision to be taken in respect of the application, taking account of Community law.

In the event of a draft decision which envisages the granting of marketing authorisation, the documents referred to in Article 31(3) of Regulation No. 2309/93 shall be annexed.

Where, exceptionally, the draft decision is not in accordance with the opinion of the Agency, the Commission shall also annex a detailed explanation of the reasons for the differences.

A final decision on the application shall be adopted in accordance with the procedure laid down in Article 73 of Regulation (EEC) No. 2309/93.

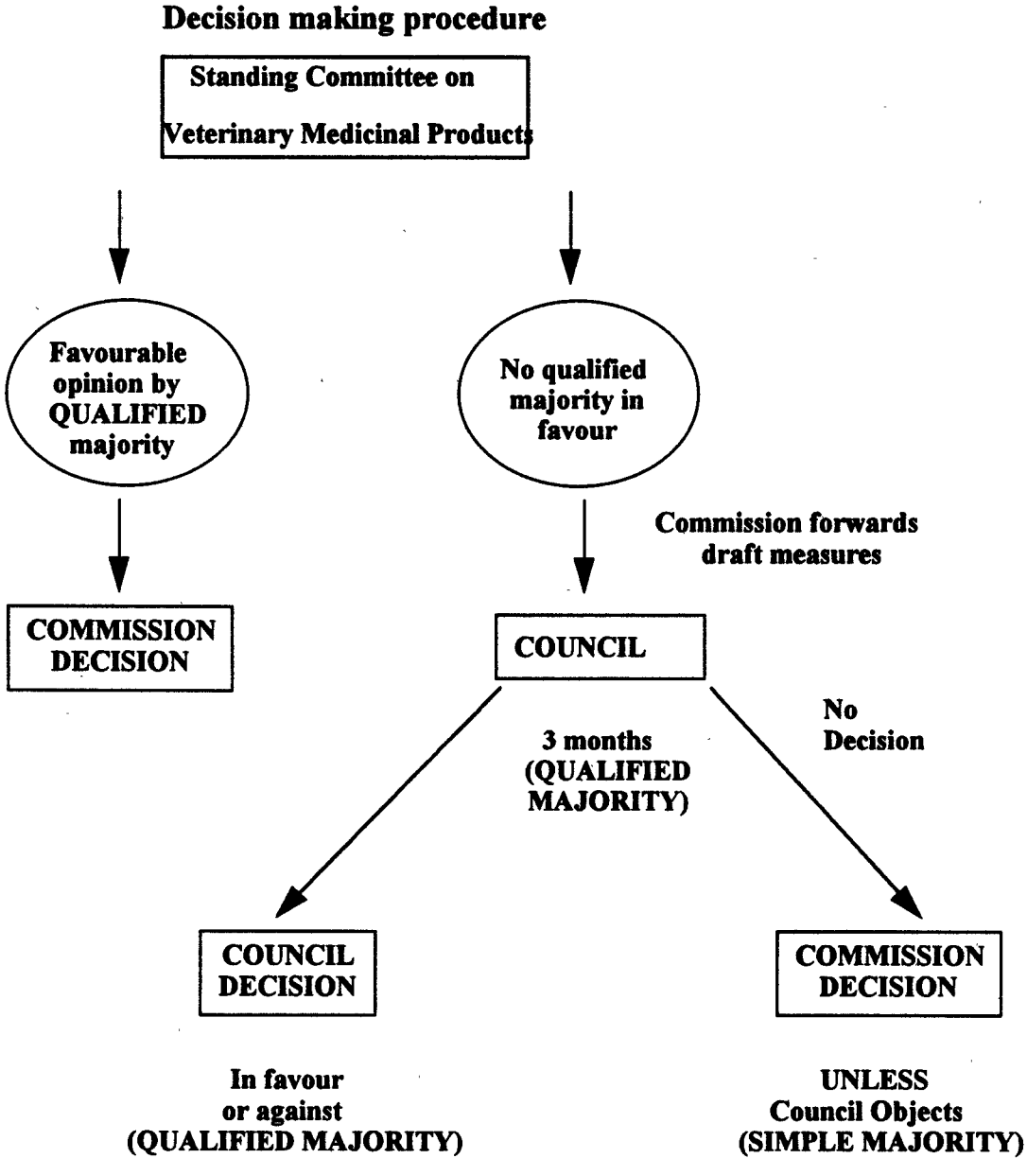
8.1 Status of a Community authorisation

Medicinal products which have been authorized by the Community in accordance with the provisions of the Regulation benefit from the ten-year period referred to in point 10 of the third paragraph of Article 5 of Directive 81/851/EEC.

Without prejudice to Article 34.1 of Regulation (EEC) Nr. 2309/93, a marketing authorisation which has been granted in accordance with the procedure laid down in this Regulation shall be valid throughout the Community. It confers the same rights and obligations in each of the Member States as a marketing authorisation granted by that Member State in accordance with Article 3 of Directive 65/65/EEC. The granting of

authorisation shall not diminish the general civil and criminal liability in the Member States of the manufacturer or, where applicable, of the person responsible for placing the veterinary medicinal product on the market.

The refusal of a Community marketing authorisation shall constitute a prohibition on the placing on the market of the veterinary medicinal product concerned throughout the Community.



8.2 Publication of the authorisation

Once a medicinal product has been authorized, it shall be entered in the *Community Register of Medicinal Products* and shall be given a Community marketing authorisation number which must appear on the packaging. Appropriate notification of marketing authorisation shall be published in the *Official Journal of the European Communities.*

8.3 European Public Assessment Report

In accordance with Article 34.4 of Regulation (EEC) No. 2309/93, and upon request from any interested person, the Agency shall make available the assessment report of the veterinary medicinal product by the Committee and the reasons for its opinion in favour of granting authorisation, after deletion of any information of a commercially confidential nature.

This document (called the European Public Assessment Report or EPAR) is based upon the assessment report which accompanied the opinion of the scientific committee. Applicants are reminded that the assessment report may include parts of the written summaries of the Expert Report.

8.3.1 Operating approach to the preparation of the EPAR

In order to prepare its opinion, the Committee will, in the course of developing its assessment report, consider the assessment report which will accompany the opinion of the Committee. Generally the assessment report will be endorsed by the Committee at the same time as the opinion. The task of combining and presenting the EPAR will fall to the secretariat of the Agency.

8.3.2 Commercial confidentiality:

In accordance with Article 31.3 of the Regulation, the applicant will receive the assessment report of the Committee.

Thus, the applicant should be in a position to identify within a short period of time (for example 30 days) those issues which they consider to be commercially confidential.

Upon receipt of the applicant's response with those issues which the applicant considers to be commercial confidentiality, the Agency will prepare a final text of the EPAR, taking into account the obligations of the regulation, transparency and confidential considerations.

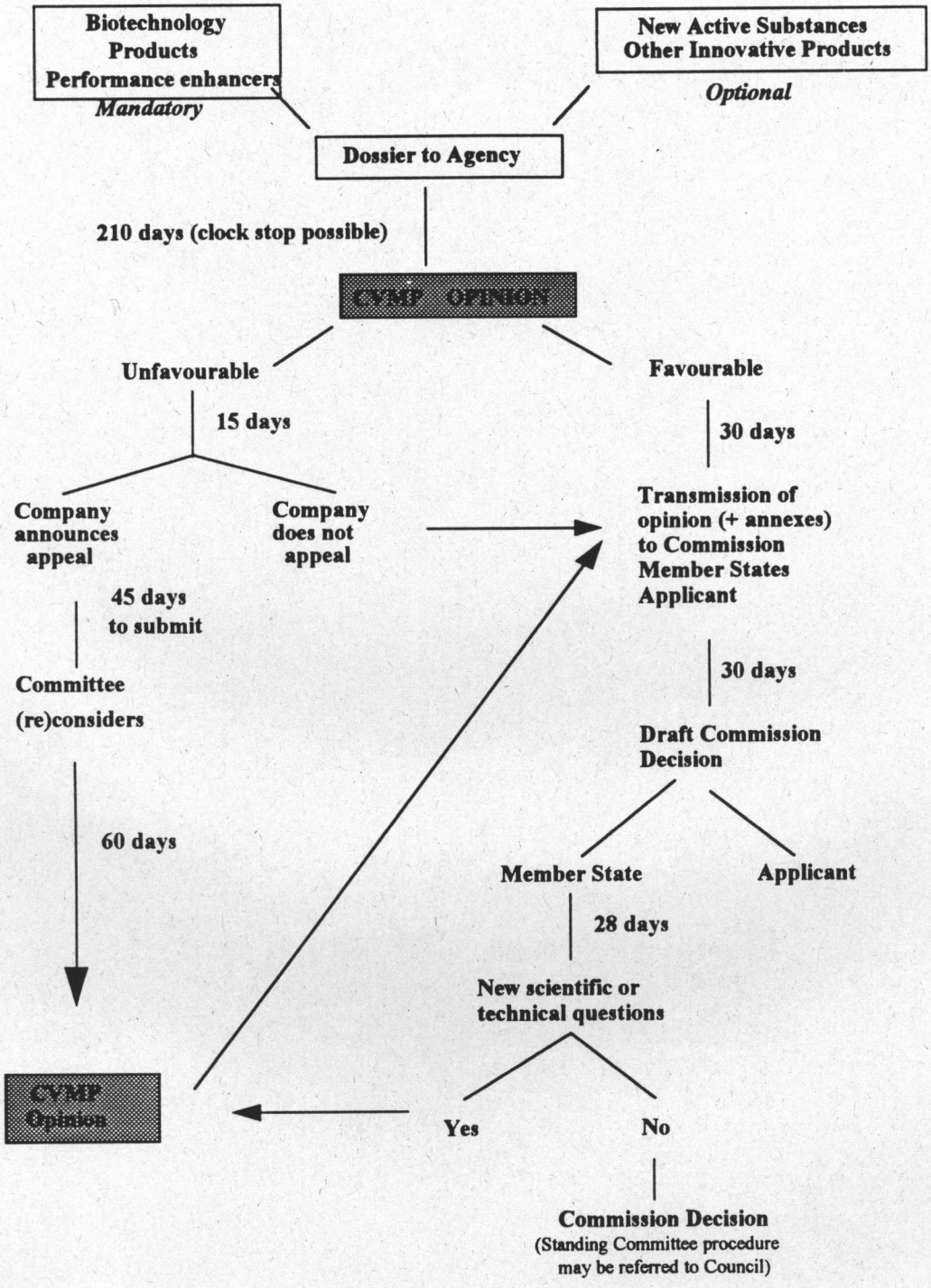
The final EPAR would be submitted to the Committee for Veterinary Medicinal Products prior to being made available, upon request.

8.3.3 Availability

Normally, the EPAR would be available at the same time as the Commission decision on the application (and a standard statement to this effect will be included in the O.J. publication).

The EPAR is available upon request - requests would be submitted in writing. At regular intervals, a compilation of the requests for the EPAR of a given veterinary medicinal product would be made available to the marketing authorisation holder.

CENTRALISED PROCEDURE



CHAPTER V

PHARMACOVIGILANCE OF VETERINARY MEDICINAL PRODUCTS

1. LEGAL BASIS AND PURPOSE

The legal framework for pharmacovigilance of veterinary medicinal products in the Community is given in Council Regulation (EEC) No 2309/93 (Title 3, Chapter III) and Council Directive 81/851/EEC as amended by Council Directive 93/40/EEC.

Pharmacovigilance activities come within the scope of the criteria of quality, safety and efficacy, as new information is accumulated on the veterinary medicinal product under normal conditions of use in the marketing situation. Pharmacovigilance obligations apply to all authorised veterinary medicinal products.

Council Regulation No 2309/93 (Articles 19 to 22) and Directive 93/40/EEC (Chapter VI Articles 42a to 42d describe the respective obligations of the person responsible for placing the medicinal product on the market and of the competent authorities to set up a system for pharmacovigilance in order to collect, evaluate and collate information about suspected adverse reactions. All relevant information should be shared between the competent authorities and the person responsible for placing the veterinary medicinal product on the market, in order to allow the partners in pharmacovigilance activities to assume their obligations and responsibilities. This requires an exchange of information between the Agency, the Member States, and the person responsible for placing the medicinal products on the market, as well as procedures to avoid duplications, maintain confidentiality and ensure the quality of the systems.

The person responsible for placing the veterinary medicinal product must ensure that they have an appropriate system of pharmacovigilance in place in order to assure responsibility and liability for their products on the market and to ensure that appropriate action can be taken, when necessary.

In accordance with Article 46 of the Regulation and Article 42g of the Directive, guidance for marketing authorisation holders on the implementation and practical procedures involved in complying with the above legislation, in the interests of protecting public health, have been prepared. The following areas are covered:

1.1 Responsibilities of marketing authorisation holders

The responsibilities of the qualified person responsible for pharmacovigilance are as follows:

i) the establishment and maintenance of a system which ensures that information about all suspected adverse reactions which are reported to the personnel of the company, including to medical representatives, is collected and collated so that it may be accessed at a single point within the Community;

ii) the preparation for the EMEA and competent authorities of Member States where the medicinal product is authorised of the reports referred to in the Regulation and Directive and further detailed in this chapter:

- Adverse reaction reporting
- Periodic safety update reporting
- Post-authorisation safety studies
- Ongoing risk/benefit evaluation during the post-marketing period

iii) Ensuring that any request from the competent authorities for the provision of additional information necessary for the evaluation of the benefits and risks afforded by a medicinal product is answered fully and promptly, including the provision of information about the volume of sales or prescriptions of the medicinal product concerned.

The person responsible for placing the medicinal product must ensure that they have an appropriate system of pharmacovigilance in place in order to assure responsibility and liability for their products on the market and to ensure that appropriate action can be taken, when necessary.

1.2 Pharmacovigilance guidelines

In accordance with Article 46 of Regulation (EEC) Nr. 2309/93 and Article 42g of Directive 81/851/EEC, guidance for marketing authorisation holders on the implementation and practical procedures involved in complying with the above legislation, in the interests of protecting public health, have been prepared. The following areas are covered in this chapter:

Section 2 Adverse reaction reporting

Section 3 Periodic safety update reporting

Section 4 Company sponsored post-authorisation safety studies

Section 5 Ongoing risk/benefit evaluation during the post-marketing period

2. ADVERSE REACTION REPORTING

The marketing authorisation holder is responsible for reporting suspected adverse reactions to the authorities of the Member States and European Medicines Evaluation Agency (EMEA) for their veterinary medicinal products authorised under the centralised procedures and to the appropriate authorities of the Member States for their medicinal products authorised through the national procedure.

2.1 Scope

The scope of veterinary pharmacovigilance is considered to be broader than in pharmacovigilance of medicinal products for human use, covering not only clinical safety but misuse of a product, epidemio-surveillance of resistances or environmental problems.

For veterinary medicinal products authorised in the Community (whether through the centralised or national procedures): suspected adverse reactions received from veterinarians, animal owners or users of the veterinary medicinal product should be reported. These should be reported even if the marketing authorisation holder does not agree with the reporter's

assessment of a possible causal association. Spontaneously reported suspected adverse reactions, suspected adverse reactions from post-marketing surveillance studies and those reported in the world-wide literature are included.

Adverse "events" which are not suspected of being product-related by the veterinarian, animal owner or other person responsible for the animal should not be reported unless the marketing authorisation holder has reason to believe that a causal relationship is possible.

If the marketing authorisation holder is aware that a reporter has reported a reaction to one of its products directly to the authority of a Member State, the marketing authorisation holder should still report the reaction, informing the authority that the report is likely to be a duplicate of a previous report. In this situation it is essential for the marketing authorisation holder to provide all the available details including any authorisation number provided to the reporter by the authority, in order to aid identification of the duplicate.

Marketing authorisation holders are expected to fully validate and follow-up all serious reactions reported by them to the authorities. All available clinical information relevant to the evaluation of the reaction should be provided.

2.1.1 Spontaneous ADR reports and case reports from the world-wide literature

i) Spontaneous ADR reports occurring in the EC

The marketing authorisation holder should report all suspected serious adverse reactions occurring within the Community and brought to its attention. These should be reported immediately and in no case later than 15 calendar days from receipt to Member States in whose territory the incident occurred. Any suspected increase in the frequency of serious reactions should also be reported. The basis on which the frequency assessment has been made should be provided. All other reactions should be reported as line listings on request or at 6-monthly intervals for 2 years post-authorisation, yearly for the subsequent 3 years and at the 5-yearly renewal.

ii) Spontaneous ADR reports occurring outside the EC

The marketing authorisation holder should report all suspected serious and unexpected adverse reactions occurring in the territory of a third country and brought to its attention. These should be reported to all Member States and the EMEA immediately and in no case later than 15 calendar days following receipt. All other suspected adverse reactions should be reported as line listings on request or at 6-monthly intervals for 2 years post-authorisation, annually for the 3 subsequent years and at the 5-yearly renewal.

iii) Case reports from published scientific literature

The marketing authorisation holder is expected to screen the world-wide literature and report published suspected adverse reactions in relation to the active substances(s) of its veterinary medicinal products, as relevant to the categories identified in (i) and (ii) above. A copy of the relevant published Article should be provided, if necessary, translated into a language acceptable to the Member State.

2.1.2 Reports from post-authorisation studies

Compared to human medicine, the tolerance of veterinary drugs is more predictable since it is studied in the target species at supra-therapeutic doses, which allows for the evaluation of a margin of safety.

Therefore the need for post-authorisation surveillance studies is certainly not so stringent in the veterinary field. Spontaneous reporting schemes provide the complementary information concerning adverse drug reactions, especially those which are unexpected.

However, for specific cases concerning for example the occurrence of pathological events that could be drug-related (such as mastitis after intra-mammary infusion) or post-vaccinal reactions, post-authorisation studies should be envisaged.

The methodology for such studies is obviously quite specific to the veterinary field and should be considered as an interesting area of investigation in veterinary pharmacovigilance.

Besides those sponsored by the company, post-authorisation studies might also include those reported by veterinary practitioners, centers of veterinary pharmacovigilance and specialists in epidemiological and clinical sciences.

Suspected serious adverse reactions from post-authorisation studies should be reported to all Member States. These should be reported immediately and in no case later than 15 calendar days from receipt. Non-serious reactions should be reported in summary at the end of each study.

Adverse events not suspected to be due to the study product should not be reported as individual cases.

2.1.3 Minimum requirements for an ADR Report to be recorded by the marketing authorisation holder, and reported to the Member State

A case report will be considered as an adverse reaction report provided that at least the following data are available :

(i) An identifiable source, wherever possible this should include the name and address of the reporter (e.g. veterinarian, pharmacist, animal owner)

(ii) animal details : species, gender, age

(iii) suspect drug

(iv) suspected reaction

The reference point for deadlines for submission of reports is the time of receipt of the minimum information. It should be stressed that these are minimum requirements and that companies should endeavour to provide all the information necessary for a full evaluation.

2.2 Additional information to be reported within the frame of pharmacovigilance

2.2.1 Extra-label use (unlicensed use of products)/Misuse/Abuse

Occasionally reports may be obtained on products used outside the terms of the marketing authorisation e.g. use of a product in non-authorised species or use at doses differing from those set out in the package insert.

While this practice is neither endorsed nor recommended, such reports can provide useful information on the safety of the product and should be recorded by the person responsible for pharmacovigilance and reported to the competent authorities in the normal way.

The system shall also collate information on frequently observed misuse and serious abuse of veterinary medicinal products.

2.2.2 Reporting of human reactions to veterinary medicinal products

Suspected adverse reactions occurring in humans following use of veterinary medicinal products should be reported promptly to the competent authorities.

2.2.3 Reporting of lack of efficacy reports

Directive 81/851/EEC cites the lack of therapeutic effect as a reason for refusal of authorisation. It is incumbent therefore for companies to investigate such reports.

Where the conclusions drawn from the reports differ from those in the dossier on which the authorisation was granted and which might normally be expected, the company should inform the competent authority.

Lack of efficacy in this context means : no therapeutic efficacy of a veterinary medicinal product or no efficacy according to the indications claimed for, leading to the development, spreading or deterioration of a disease.

2.2.4 Medicated premixes

When medicated premixes which have been incorporated in the finished feed are suspected of causing a reaction in consumers, operators or animals, both the premix and the finished feed should be investigated without delay.

Among the factors that have to be examined are the composition of the finished medicated feed, the inclusion levels of active ingredients, the operation of the milling process(es) and when possible the actual dosage administered to individual target animals.

2.2.5 Reporting of known side effects

Companies are required to maintain a record of all adverse reactions reported to them, whether or not previously known (i.e. indicated on the package insert or data sheet).

Where possible, the incidence of such reports should be established in comparison with the number of doses sold. Where the incidence is greater than that established in the dossier on which the authorisation was granted, the competent authority must be informed.

2.2.6 Reporting of insufficient withdrawal periods

Information on insufficient withdrawal periods is deemed important for pharmacovigilance purposes as residues of veterinary medicinal products in food derived from animals can be a hazard to human health or a problem to processing of animal products (e.g. milk).

2.3. Content of suspected serious ADR reports

It is essential for the marketing authorisation holder to provide as complete as possible details for cases of suspected serious ADRs in order to facilitate assessment. The marketing authorisation holder is expected to follow-up all reports of serious suspected adverse reactions to their products in order to obtain comprehensive information where available. The report of a suspected ADR should include the information below. The words used by the reporter should be provided even if they are also classified or coded according to accepted terminology.

2.3.1 Animal details

i) Number treated / number showing signs / number dead;

ii) Characteristics of animals showing signs :
- species
- Breed
- Gender
- Age
- Weight

2.3.2 Company details and original reporter's details

i) The name of the qualified person responsible for pharmacovigilance employed by the marketing authorisation holder.

ii) Address, telephone and fax number of the qualified person.

iii) MA number for the suspected product.

iv) Country of origin of the report, and country of origin of suspect product if different from that of the report.

v) Type of report, *e.g.* spontaneous, post-marketing study, literature.

vi) Source of report.

vii) Details of the original reporter – name (if acceptable under national law), address, profession and speciality (if available).

viii) Date of receipt of report by marketing authorisation holder.

2.3.3 Suspect product details

i) Product name(s) / brand name(s)

ii) Approved name(s) (INN)

iii) Batch number, if appropriate

iv) Indication(s) for treatment

v) Dose, frequency and duration of treatment given

Dose, frequency and duration of treatment recommended

vi) Route and site of administration used

Route and site of administration recommended

vii) Start date / time

viii) Stop date / time and/or duration of treatment

ix) Dechallenge information

x) Re-challenge information

2.3.4 Concomitant medication details

All medicinal treatment over at least a one week period preceding the suspected reaction should be provided when available. This should also include non-prescription medicines and magistral preparations if appropriate. For each medication:

i) Medicinal product name(s)/brand name(s)

ii) Approved name(s) (INN)

iii) Batch number, if appropriate

iv) Indication(s) of treatment

v) Daily dose, frequency and duration of treatment

vi) Route of administration

vii) Start date/time

viii) Stop date/time and or duration of treatment.

2.3.5 Suspected reaction details

i) Description of reactions(s) including site and severity (intensity of the reaction)

ii) Start date or onset of reaction

iii) Stop date or duration of reaction

iv) Outcome - information on recovery and its extent, whether associated with product withdrawal and whether specific treatment was required. In a case of fatal outcome, the cause of death should be provided and its relationship to the suspected reaction commented upon. Post mortem examination findings or laboratory findings, if carried out, should be provided.

It should be noted that death is not an ADR but an outcome. However, when the cause of death is unknown the term "sudden unexplained death" may be used to describe a reaction.

2.3.6 Other Information

Any relevant information available to facilitate assessment of the case should be provided, such as previous exposure, disposition to allergy, feed given/changes in feeding habits, concomitant use of medicated feedstuffs.

2.3.7 Scientific Evaluation (causal assessment)

Marketing authorisation holders may comment on whether they consider there is a causal association between the suspect product(s) and reactions(s) reported and should provide the criteria on which they have made the assessment.

The causality assessment should be done using the ABO-system if possible. According to this system, four categories of causality can be made:
category "A": probable
category "B": possible
category "O": unclassified (cases where insufficient information was available to draw any conclusion)
category "N": unlikely to be drug related (cases where insufficient information was available and where investigation has established this beyond reasonable doubt (document III/3578/91)

2.3.8 Human reactions to veterinary medicinal products

Information about any reactions in humans as a result of administering veterinary medicinal products should be given with at least the following details :

i) Animal identification, if available

ii) Gender

iii) Age or date of birth

iv) Nature of exposure (e.g. inhalation, injection, ingestion or dermal exposure)

v) Nature of reaction

vi) Time between exposure and reaction

vii) Outcome of reaction (e.g. extent of recovery, specific treatment required)

viii) Name, address, telephone number of physician or poison center if consulted

2.4 Reporting forms

Until a standardised reporting form is agreed, reporting forms acceptable to the Member State authorities should be used. An example of a reporting form is attached at Table A. Computer-generated forms are acceptable provided they are legible and follow the accepted content and layout.

2.5 Impact of reported ADRs on the overall safety profile and summary of product characteristics of a product

The marketing authorisation holder should indicate when reported ADR(s) impact on the established safety profile of the product, in particular when the reported reaction is unexpected or when there is a suggestion of a change in the nature, severity or frequency of expected ADRs or when new risk factors are identifiable. Information on the frequency of ADRs should provide the basis on which the estimate has been made, including data on the total number of ADR reports and animal exposures.

In situations where reported ADRs do impact on the established safety profile, the marketing authorisation holder should indicate what action is proposed.

3. PERIODIC SAFETY UPDATE REPORTS

A Periodic Safety Update report is intended to provide an update of the world-wide safety experience of a veterinary medicinal product to competent authorities at defined times post-

authorisation. At these times marketing authorisation holders are expected to provide succinct summary information together with a critical evaluation of the benefit/risk of the product in the light of new or changing post-marketing information, in order to ascertain whether further investigations need to be carried out and whether changes should be made to the SPC, labelling or product promotion. Safety update reports for veterinary medicinal products authorised under the centralised procedure should be submitted to all the competent authorities of Member States and the EMEA in accordance with Regulation (EEC) No 2309/93 Articles 43 and 44 and for veterinary medicinal products authorised nationally to the competent authorities of the Member States in accordance with Directive 81/851/EEC Articles 42a and 42d.

3.1 Scope and frequency of reports

Unless otherwise required by the licensing authority, a periodic safety update summary report, in the specified format, should be prepared for all authorised medicines at the following intervals:

- 6-monthly for the first 2 years after authorisation
- annually for the subsequent 3 years
- thereafter 5-yearly at the time of renewal.

Each safety update report should cover the period of time since the last update report and should be submitted within 60 days of the data lock point.

Each medicinal product will have an EC birth date, which will be the date on which the product was first approved in the EC. The year of the EC birth date determines the start of submission of periodic safety updates (6 months, annually and 5 yearly). However, some flexibility may be used in order to harmonise periodic safety updates internationally. Thus the month for data lock may be +/- six months within the EC birth date, provided that the first periodic safety update is submitted not later than 6 months after the EC birth date e.g.

	EC birth date	Periodic Safety Updates
	May 1995	
	↓	
International birth date	Sept. 1993----------	----------Sept '95, March '96 etc.

For the purpose of the safety update report the marketing authorisation holder's database should be frozen in relation to the product at the time points defined above. These are the data lock points (DLPs). Up-to-date safety data, i.e. data that becomes known to the marketing authorisation holder after the product's DLP and which may influence the evaluation should also be included in the report in the final section. Data relating to serious adverse reactions must also be reported separately from the safety update report.

The report should include a cross reference to combination products, where appropriate, with reference to the active substance. It will be necessary, in a given report, to separate different formulations, routes of administration, and indications, if this information is available. When relevant, the safety update should also differentiate data associated with salient pharmaceutical aspects, including the active moiety or moieties, excipients, strength(s) and dosage form(s), etc.

3.2 Content of Safety Updates

A Safety Update report should be written in English and fulfil the following format and content (for products authorised under a national procedure, the language requirements of the member State apply):

3.2.1 SPC

The EC SPC must be included for reference in the report. If no SPC is available, the package insert should be provided.

3.2.2 The product's authorisation status world-wide

Brief information should be provided, usually as a table, on all countries in which a regulatory decision about marketing has ever been made (*e.g.* approved, approved with qualifications, rejected, etc.). This should be divided into EC and non-EC countries and presented in order of date of regulatory decision.

Besides listing the dates of approval (or rejection) the date of market introduction (launch date) should also be given. The table should also give the "trade names" used by the marketing authorisation holder or affiliates in the different countries where the product has been launched and to which this report refers. Approved indications for use may differ among countries, and details should be provided if they are relevant to interpretation of clinical safety information. This section (Section III) of the report is the only one that is cumulative.

3.2.3 Update of regulatory or marketing authorisation holder actions taken for safety reasons

An update on the significant regulator-initiated or marketing authorisation holder-initiated actions taken, or to be taken, for safety reasons during the report period anywhere in the world should be presented. This should include: product suspension; restrictions on distribution; any curtailment of trial programmes; alterations to label/SPC/Package insert such as new contraindications, warnings or addition of important adverse drug reactions, lowering of recommended dosage; pharmaceutical changes, *e.g.* change of excipients, changes in the manufacturing process.

The format should be a brief narrative stating the reasons for significant regulatory or marketing authorisation holder action, with documentation appended when appropriate.

3.2.4 Sales volume

A safety update must address the relationship of sales volume of a product related to numbers of suspected adverse reactions reported. Where a single species can be associated with use of pharmaceutical product, then the incidence of reactions and deaths can be calculated in terms of the number of single doses of the drug used in animals of x kg. Simple calculations from the data sheet (SPC) will give the number of animals treated after a course of treatment with the product. Where products are continually administered the calculation of incidence of reactions and deaths has to be calculated in an arbitrary manner (medicated premixes).

In the case of vaccines, sales volume should be expressed as single booster doses for a particular species.

A proportion of veterinary medicines are indicated for more than one species. Where such a situation pertains it is clearly not possible to calculate individual species incidence of reactions. Theoretical calculations for single species are sometimes of value, but should always be treated as arbitrary. A significant number of safety updates will show no reports of suspected adverse incidents. In these cases it is not possible to calculate an incidence of reactions.

3.2.5 Individual case histories

Each safety update report should contain the number of doses sold expressed in an appropriate form relating to the member state who requested the report. In addition, the report must include the incidence of reactions over the period of the report, taking account of doses sold in the member state.

The minimum information constituting a reportable individual case (line listing) includes :

1. Licence number
2. Company case reference number
3. Date of reaction
4. Number of animals treated
5. Species
6. Age(s)
7. Number reacting (approximate)
8. Number dying
9. Other products, including authorised medicated premixes, used concurrently
10. Presenting signs
11. Conclusions, comments and causality assessment

The appropriate individual case histories defined below should be included only if received during the period of review. All should be presented in the line-listing format given in Table B.

a) Spontaneous reports

All individual case reports sent spontaneously to the MA holder and attributed to the drug which relate to all reactions, including interactions and extra-label use, should be submitted. These should include those received from regulatory authorities.

b) Serious case reports from other sources

Marketing authorisation holders sometimes receive ADR information on individual incidents from other sources, including regulatory authorities; those from regulatory authorities should also be listed, identifying their source. A signal generated on the basis of these case reports should be reported in the narrative with sufficient case information. The aim is to be comprehensive but to avoid duplication of reporting.

c) Line listing

All the required individual case reports should be presented as line listings, in the format as shown in Table B.

The following information, where available, should be included for each case in addition to the minimum information, previously detailed, for each case:

- Date of treatment / Date of vaccination
- Was the product used as recommended?

The line listing should also include all serious reactions that qualified for reporting by MA holders as full 15 day reports under the guidelines on adverse reaction reporting by MA holders. These cases should be identified (e.g. asterisked) in the conclusions/comments section of the line listing.

d) Narrative review of the individual case histories

The report should include a brief narrative based on the marketing authorisation holder's analysis of the cases presented in the line listing. This should include a comment on any increase in frequency.

3.2.6 Published ADR reports

A brief narrative overview with a bibliography of published ADR reports should be attached to the copies of the full report.

3.2.7 Overall safety evaluation

The safety update should include a concise critical analysis and opinion on the benefit/risk profile of the product written by a person responsible for pharmacovigilance. Any new important information on the following should be explicitly included:

i) evidence of previously unidentified toxicity

ii) increased frequency of known toxicity

iii) drug interactions

iv) overdose and its treatment

v) extra-label use

vi) human operator reactions

For each of these points, lack of significant information should be reported.

The evaluation should indicate in particular whether the safety data remain in line with the cumulative experience to date and the SPC, and should specify any action recommended and the reasons why.

3.2.8 Important information received after data lock-point

This section is for reporting any important new information received by the marketing authorisation holder since the database was frozen for review. It may include significant new cases or follow-up data that affect the interpretation or evaluation of existing reports. The impact of this information on the overall safety evaluation should be discussed.

4. ON-GOING PHARMACOVIGILANCE EVALUATION DURING THE POST-AUTHORISATION PERIOD

The granting of a marketing authorisation for a veterinary medicinal product indicates that it is considered to have a satisfactory balance of benefits and risks under the conditions defined in the Summary of Product Characteristics (SPC), on the basis of the information available at that time.

During the post-marketing period the product will be used in a different setting from clinical trials and larger populations are likely to be exposed. Much new information will be generated which may impact on the benefit/risk ratio and evaluation of this needs to be an on-going process, both within pharmaceutical companies and regulatory authorities.

The purpose of pharmacovigilance is to protect animal and public health and the environment, and new information relating to the safety of marketed veterinary medicinal products may

become available at any time. Therefore marketing authorisation holders and competent authorities have a responsibility to ensure that the balance of benefits and risks for marketed veterinary medicinal products remains favourable, that appropriate action must be taken in response to new evidence which impacts on this balance, and that the necessary information in relation to these matters must be available to competent authorities and marketing authorisation holders, and through product information to prescribers and users of the veterinary medicines.

Thus it is considered useful to:

i) Define the steps that need to be taken by pharmaceutical companies to ensure that veterinary medicinal products marketed within the EC are subjected to adequate ongoing monitoring and benefit/risk evaluation during the post-authorisation period.

ii) Provide guidance on interactions between pharmaceutical companies and regulatory authorities (both the EMEA and national competent authorities) on matters related to on-going post-authorisation benefit/risk evaluation.

iii) Provide the principles on which actions taken to improve the benefit/risk ratio should be based.

5. OVERALL BENEFIT/RISK EVALUATION

Benefit/risk evaluation is the process by which the benefits and risks of a veterinary medicinal product are assessed and balanced.

Benefit/risk evaluation of all marketed veterinary medicinal products should be carried out using multiple sources of data, principally the following (where available):

i) Spontaneous ADR reporting data from within the EC

ii) Spontaneous ADR reporting data from outside the EC

iii) Post-authorisation safety studies

iv- World-wide published scientific literature

v) Product usage

In the event of any new or changing information becoming available which impacts on, or may influence the overall benefit/risk evaluation of a veterinary medicinal product, the marketing authorisation holder should immediately inform all the competent authorities in countries in which the product is authorised and in addition, for products which are authorised centrally, the Commission and the EMEA. A comprehensive report evaluating the issue and the risks in the context of the benefits should be submitted at the earliest opportunity and no later than 4 weeks of being requested, to all competent authorities of the Member States in which the medicine has been authorised and in addition, for products which are authorised centrally, the Commission and the EMEA.

Improving the balance of benefits and risks

The following types of action may be necessary and can be undertaken voluntarily by marketing authorisation holders or compulsorily by competent authorities in accordance with their legal powers:

i) Variation of the SPC in respect of the indications, dosage recommendations, contraindications, warnings or adverse effects and in consequence:
- modification of the package insert
- modification of advertising material.

ii) Direct provision of important safety information to health professionals (*e.g.* through letters and/or bulletins).

In cases of urgency where there is a risk to animal or public health or the environment, marketing authorisation holders may make urgent safety restrictions in accordance with Regulation XXX/95. These measures must be communicated without delay to the EMEA and Member States, and an application for approval submitted to the relevant authorities within 24 hours of their introduction.

When any significant alteration to the safety information in an SPC is made, the appropriate health professionals must be informed promptly and circulated with the new SPC either directly or by publication of the new SPC in the medical press. The package insert should also be updated and made available with the product. The time scales for ensuring that information is available to product users should be agreed with the competent authorities of Member States and EMEA.

In the event that the overall benefit/risk ratio is judged to be unacceptable even after the effect of any appropriate action is taken into account, the medicine should be withdrawn from the market and the appropriate veterinarians, pharmacists and animal owners informed. Such action may be taken voluntarily by companies. The appropriate competent authorities must be informed and consulted immediately the decision has been taken by the holder of the marketing authorisation.

In the event that the overall benefit/risk ratio is judged to be unacceptable even after the effect of any appropriate action is taken into account, the EMEA or any national regulatory authority may immediately suspend the marketing authorisation in the following circumstances:

i) there appears to be an urgent hazard for public or animal health or the environment which cannot be prevented by any other means;

and

ii) the holder of the Marketing authorisation has been given the opportunity to take such action voluntarily and has refused.

In this event the matter will then be reviewed urgently by the CVMP, in accordance with the procedures laid down in Council Regulation (EEC) Nr.2309/93 or Council Directive 81/851/EEC, as appropriate.

DEFINITIONS

Adverse Drug Reaction (ADR) / Adverse Reaction

Adverse drug reaction in this context is considered as synonymous with adverse reaction. Adverse drug reaction means a reaction which is harmful and unintended and which occurs at doses normally used in animals for the prophylaxis, diagnosis or treatment of disease or the modification of physiological function.

Adverse Event (or experience)

Any undesirable experience occurring to an animal treated with a pharmaceutical product whether or not considered related to the veterinary medicinal product.

Serious Adverse Reaction

This is an adverse reaction which is fatal, life-threatening, lesion-producing, disabling, incapacitating or which results in permanent or prolonged symptoms in the animals treated.

Unexpected Adverse Reaction

This relates to an adverse reaction which is not mentioned in the EC summary of product characteristics (SPC) or for non- EC countries, the national data sheet of the country in which the reaction occurred if a SPC does not exist.

EC Birth Date

This is the date on which the veterinary medicinal product was first authorised within the EC. Safety Updates should normally be prepared at the defined time points after this date.

Data Lock-Point (cut-off date)

The date designated as the cut-off date for data to be incorporated into a particular safety update. On this date the data available to the author of the safety report is extracted for review and stored.

Abuse

Persistent or sporadic, intentional excessive use or administration of a veterinary medicinal product inconsistent with or unrelated to the recommendations of the summary of product characteristics.

Misuse

Use of a veterinary medicinal product in a way which is not recommended in the summary of product characteristics, with the exception of those cases referred to in Article 4.4 of Directive 81/851/EEC.

TABLE A

INDIVIDUAL REPORT FORMAT FOR SUBMISSION TO COMPETENT AUTHORITIES

(One form per product used)

Case reference number :

Date of report to company :

PRODUCT NAME :

Composition :

Authorisation number :

Manufacturer :

Batch number :

Expiry date :

OTHER PRODUCTS USED (Name and Active Ingredients)

Date of treatment :

Date of onset of unexpected signs :

Route and site of administration used :

Route and site recommended :

Dose frequency and duration of treatment given :

Dose frequency and duration of treatment recommended :

Diagnosis/Reason for treatment :

Authorised indication for use :

TYPE OF SAR (e.g. extra label, human reaction, lack of efficacy, licensed use) :

ANIMAL DETAILS

No. treated No. showing signs

Characteristics of animals showing signs :

Species : Breed :
Sex : Age :

Weight :

NATURE OF REACTION (describe the sequence of events, all clinical signs and other relevant observations) :

Time between administration and reaction :

OUTCOME OF REACTION TO DATE : Date :

	Killed/Dead	Under Treatment	Alive with Sequelae	Recovered	Unknown
No. of animals					

Had animals had previous exposure to this product ?

If affirmative, were similar signs seen ?

Were the unexpected signs treated ? If yes, describe :

POST MORTEM OR LABORATORY FINDINGS :

NATURE OF COMPANY INVESTIGATION :

SUMMARY OF PRODUCT SAMPLE INVESTIGATION :

Product source : Type of analysis : Result :

CONCLUSIONS/ACTION TAKEN :

CAUSALITY ASSESSMENT :

Name and signature of company investigator :

Date :

IN CONFIDENCE **TABLE B**

VETERINARY PHARMACOVIGILANCE SCHEME

COMPANY/LICENCE HOLDER FORM FOR MULTIPLE REPORTS OF SUSPECTED ADVERSE REACTIONS

COMPANY/LICENCE HOLDER

PRODUCT : **LICENCE NO. :**

PERIOD OF REPORT FROM —/—/— TO —/—/— **No. OF DOSES DURING PERIOD OF REPORT :** **INCIDENCE :**

COMPANY CASE REF	DATE OF TREATMENT/ VACCINATION	DATE OF REACTION	NO. TREATED	SPECIES AND AGE (Juv/Adult)	NO. REACTED	NO. DIED	WAS PRODUCT USED AS RECOMMENDED YES/NO	OTHER PRODUCTS USED CONCURRENTLY	PRESENTING SIGNS/ DIAGNOSIS	COMPANY CON-CLUSIONS AND COMMENTS
TOTAL										

FOR NATIONAL PHARMACOVIGILANCE USE ONLY

REFERENCE : DATE OF RECEIPT : NUMBER OF INCIDENTS :

CHAPTER VI

VETERINARY MEDICINAL PRODUCTS CONSISTING OF OR CONTAINING GENETICALLY MODIFIED ORGANISMS

This chapter contains three separate guidance documents relating to the environmental risk assessment which must accompany applications for marketing authorisation of veterinary medicinal products which consist of or contain genetically modified organisms (GMOs)[1].

Guidelines for the environmental risk assessments of non-GMO containing veterinary medicinal products are under development and should be completed by the end of 1995.

Guideline on the presentation of particulars concerning the environmental risk assessment for veterinary medicinal products which contain, or consist of, genetically modified organisms.

1. INTRODUCTION

This text provides detailed guidance on the form in which the particulars relevant to the environmental risk assessment are to be presented by the applicant as part of his/her application for authorisation to market a medicinal product for veterinary use which contains, or consists of, a genetically modified organism (GMO) It is important to distinguish carefully between products which contain substances simply derived from genetically modified organisms, and those products which contain, or consist of, such organisms. While advanced methods of genetic modification such as recombinant DNA technology have been applied in several instances to micro-organisms for the purpose of producing drug substances from them, micro-organisms which have been genetically modified by such means, and retain a capacity for replication, have only rarely themselves been developed for administration to animals for therapeutic or diagnostic purposes. As

[1]Note: This guidance does not apply to products which are made using genetically modified organisms but which, by virtue of the manufacturing method and with appropriate validation, do not contain or consist of GMOs

applications are foreseen in the field of veterinary vaccinology (including vaccines formulated as bait and intended for dissemination in an open environment) it is assumed that any affected products will be Immunological Veterinary Medicinal Products, as defined by Directive 90/677/EEC.

Council Directive 90/220/EEC on the deliberate release into the environment of genetically modified organisms requires that applicants wishing to place on the market a product which contains, or consists of, a Genetically Modified Organism (GMO) shall submit a notification for evaluation to an appropriate competent authority designated for carrying out the Directive's requirements. These provisions do not, however, apply to products containing, or consisting of, GMOs covered by other Community legislation which provides for a specific environmental risk assessment similar to that laid down in the Directive. Where a notification is required by the Directive, it must include at least the following:

- specified information relating to the product and the release (Annex IIA of the Directive), including any relevant data arising from previous releases involving research and development, and an environmental risk assessment, and

- details of any proposed conditions for placing on the market of the product (Annex III of the Directive), including conditions related to use, handling, labelling and packaging where relevant.

The notification is evaluated according to defined procedures. Deliberate release may proceed only if the applicant receives a formal consent, and is subject to any conditions specified in the consent.

However, where it is the case that the GMO constitutes, or more likely is contained in, a medicinal product, then, following from provisions appearing in Article 28 of *Council Regulation (EEC) No. 2309/93 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products:*

- the above particulars shall accompany the application for authorisation to market a medicinal product;

- these particulars shall include in addition a copy of any previously obtained written consent or consents for deliberate release for research and development purposes;

- as these requirements provide for a specific environmental risk assessment similar to that laid down in Directive 90/220/EEC, the provisions of the Directive relating to placing a medicinal product on the market no longer apply; (it should be noted that the provisions of the Directive relating to research and development or any purpose other than placing a medicinal product on the market continue to apply where relevant); and

- during the process of evaluating applications for marketing authorisations for such products, necessary consultations will be held by the rapporteur with those bodies set up by the Community or the Member States in accordance with Directive 90/220/EEC.

2. DEFINITIONS

The definitions which appear in European Community law apply. The following extracts from these are intended for the purpose of introduction only.

Medicinal Product: any substance or combination of substances presented for preventing or treating disease in human beings or animals.

Immunological Veterinary Medicinal Product: a veterinary medicinal product administered to animals in order to produce active or passive immunity, or to diagnose the state of immunity.

Organism: any biological entity capable of replication or of transferring genetic material.

Genetically Modified Organism (GMO): an organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.

Deliberate Release: any intentional introduction into the environment of a GMO or a combination of GMOs without provision for containment such as physical barriers or a combination of physical barriers together with chemical and/or biological barriers used to limit their contact with the general population and the environment.

Environmental Risk Assessment: the evaluation of the risk to human health and the environment (which includes plants and animals) connected with the release of GMOs or products containing GMOs.

3. GENERAL CONSIDERATIONS

3.1 It is essential that the approach to the environmental risk assessment presented by the applicant is similar to that laid down in Directive 90/220/EEC, including the relevant parts of Annexes IIA and III of the Directive. Headings in Annex IIA of the Directive have been omitted in this Note for Guidance in the cases in which it is considered that they are normally not applicable to medicinal products for veterinary use or to their placing on the market.

3.2 The particulars presented in accordance with this Note for Guidance will be in addition to the documentation already required in support of the claimed quality, safety and efficacy of the product. In the case of overlapping requirements the information should be repeated in full as necessary, though the data provided will in many cases be identical to data appearing in the remainder of the dossier. The applicant will obviously need to take care to ensure consistency in the presentation of data. The various requirements affecting tests, trials, documentation etc. stated in the *Rules Governing Medicinal Products in the European Community*, as with the rest of the dossier, apply where relevant.

3.3 The particulars submitted in accordance with this Note for Guidance should form part of the dossier submitted in support of the application for marketing authorisation, and should therefore be bound, paginated and indexed as such.

3.4 Binding, pagination and indexation should be logical and thorough as stated elsewhere in the Notices to Applicants.

3.5 The particulars outlined in this Note for Guidance should be presented in a separate volume, which physically could stand alone and which could be handled separately from the remainder of the dossier if necessary.

3.6 The applicant should indicate any information in Section II-H which he wishes to be treated as confidential, where this is allowed by Community law. The respective confidential and non-confidential parts should be appropriately marked, ideally on each page, and should be bound separately.

4. PRESENTATION OF DATA IN THE MAIN DOSSIER

The information presented in accordance with this Note for Guidance will form Part II-H of the dossier. The entries should be presented in six sections, Part II-H 1 to 6, as follows.

Part II-H: DATA RELATED TO THE ENVIRONMENTAL RISK ASSESSMENT FOR PRODUCTS CONTAINING, OR CONSISTING OF, GENETICALLY MODIFIED ORGANISMS (GMOs)

Part II-H-1. Introduction.

This should include a brief product profile and a description of, and justification for, the proposed release.

Part II-H-2. A copy of any written consent or consents of the competent authorities to the deliberate release into the environment of the genetically modified organisms for research and development purposes where provided for by Part B of Directive 90/220/EEC.

Any written consent(s) to release obtained within the Community must be submitted. It would also be useful to submit any written consent(s) to release obtained outside the Community.

Part II-H-3. The complete technical dossier supplying the information requested in Annex IIA of Directive 90/220/EEC, including the results of any investigations performed for the purposes of research and development.

The following points, which are extracts of Annex IIA of Directive 90/220/EEC, are those which are normally relevant to placing a veterinary medicinal product on the market. Headings in Annex IIA of the Directive which are considered to be normally not applicable to placing on the market, or not applicable to veterinary medicinal products, are

omitted. The notes in italics indicate where overlap is likely or not likely to occur with entries already required in other sections of the dossier submitted in support of a marketing authorisation, the Part numbers referring to those of the Notice to Applicants for Veterinary Medicinal Products (where Part I is equivalent to Part V of Directive 81/852/EEC, as amended by Directive 92/18/EEC, Part II is equivalent to Part 6, Part III to Part 7 (and 9) and Part IV to Part 8).

The applicant should add to the particulars listed below any additional items which are required by the nature or use of the GMO or the proposed release.

Similarly, not all the points included will apply in every case. It is to be expected, therefore, that individual applications will address only the particular subset of considerations which are appropriate to individual situations.

The level of detail required in response to each subset of considerations is also likely to vary according to the nature and scale of the proposed release.

I. General Information.

A. Name and address of the notifier.

The name and address of the applicant should be stated, in the form in which it already appears in Part I of the dossier.

II. Information Relating to the GMO.

A. Characteristic the recipient or (where appropriate) parental organism.

The entries should address each organism (recipient and/or parental organism) as appropriate.

1. Scientific name;

Part IIC 2.1..

2. taxonomy;

Part IIC 2.1.

3. other names (usual name, strain name, etc.);

Part IIC 2.1.

4. phenotypic and genotypic markers;

Part IIC 2.1.

5. degree of relatedness between donor and recipient or between parental organisms;

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

6. description of identification and detection techniques.

Part II C, but applicants should also note this requirement for the environment-specific entries which are not covered elsewhere in the dossier.

7. sensitivity, reliability (in quantitative terms) and specificity of detection and identification techniques:

Already required for PartIIC, but applicants should also note this requirement for the environment-specific entries which are not covered elsewhere in the dossier.

8. description of the geographic distribution and of the natural habitat of the organism including information on symbionts and hosts;

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier

9. potential for genetic transfer and exchange with other organisms;

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

10. verification of the genetic stability of the organisms and factors affecting it;

This information is required (for the recipient/parental organism) specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

11. pathological, ecological and physiological traits:

(a) classification of hazard according to existing Community rules concerning the protection of human health and the environment;

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

(b) generation time in natural ecosystems, reproductive cycle;

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

(c) information on survival, including seasonability and the ability to form survival structures, eg. spores.

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

(d) pathogenicity: infectivity, toxigenicity, virulence, allergenicity, carrier (vector) of pathogen, possible vectors, host range including non-target organism. Possible activation of latent viruses (proviruses). Ability to colonise other organisms.

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

(e) antibiotic resistance, and potential use of these antibiotics in humans and domestic organisms for prophylaxis and therapy.

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

(f) involvement in environmental processes: primary production, nutrient turnover, decomposition of organic matter, respiration etc.

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

12. Nature of indigenous vectors:

(a) sequence;

Part IIC 2.1.

(b) frequency of mobilisation;

Part IIC 2.1.

(c) specificity;

Part IIC 2.1.

(d) presence of genes which confer resistance.

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

13. History of previous genetic modifications.

Part IIC 2.1.

B. Characteristics of the vector:

1. Nature and source of the vector;

Part IIC 2.1.

2. Sequence of transposons, vectors and other non-coding genetic segments used to construct the GMO and to make the introduced vector and insert function in the GMO;

Part IIC 2.1.

3. frequency of mobilisation of inserted vector and/or genetic transfer capabilities and methods of determination;

Part IIC 2.1.

4. information on the degree to which the vector is limited to the DNA required to perform the intended function.

Part IIC 2.1.

C. Characteristics of the modified organism:

1. Information related to the genetic modification:

(a) methods used for the modification;

Part IIC 2.1.

(b) methods used to construct and introduce the insert(s) into the recipient or to delete a sequence;

Part IIC 2.1.

(c) description of the insert and/or vector construction;

Part IIC 2.1.

(d) purity of the insert from any unknown sequence and information on the degree to which the inserted sequence is limited to the DNA required to perform the intended function;

Part IIC 2.1.

(e) sequence, functional identity and location of the altered/inserted/deleted nucleic acid segments in question with particular reference to any known harmful sequence.

Part IIC 2.1.

2. Information on the final GMO:

(a) description of genetic trait(s) or phenotypic characteristics and in particular any new traits and characteristics which may be expressed or no longer expressed;

Part IIC 2.1, but more data and detail may be required in so far as the data relate to the environmental risk assessment.

(b) structure and amount of any vector and/or donor nucleic acid remaining in the final construction of the modified organism;

Part IIC 2.1.

(c) stability of the organism in terms of genetic traits;

Part IIC 2.1.

(d) rate and level of expression of the new genetic material. Method and sensitivity of measurement;

Also Part IIC 2.1.

(e) activity of the expressed proteins;

Part IIC 2.1.

(f) description of identification and detection techniques including techniques for the identification and detection of the inserted sequence and the vector;

Part IIC 2.1

(g) sensitivity, reliability (in quantitative terms) and specificity of detection and identification techniques;

Part IIC 2.1.

(h) history of previous releases or uses of the GMO;

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier. See also Part II-H-2.

(i) health considerations:

(i) toxic or allergenic effects of the non-viable GMOs and/or their metabolic products;

Part III, especially Part IIIE.

(ii) product hazards;

Part III, especially Part IIIC.8 and IIIE.

(iii) comparison of the modified organism to the donor, recipient or (where appropriate) parental organism regarding pathogenicity;

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

(iv) capacity for colonisation;

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

(v) if the organism is pathogenic to humans who are immunocompetent

- diseases caused and mechanism of pathogenicity including invasiveness and virulence;

- communicability;

- infective dose;

- host range, possibility of alteration;

- possibility of survival outside of human host;

- presence of vectors or means of dissemination;

- biological stability;

- antibiotic-resistance patterns;

- allergenicity;

- availability of appropriate therapies.

The information specified under (v) is required specifically to fulfil the requirements of the environmental risk assessment and may not appear *in Part III of the dossier in the detail which is required for the purposes of an environmental risk assessment.*

III. Information Relating to the Conditions of Release and the Receiving Environment.

A. Information on the release.

1. Description of the proposed deliberate release, including its purpose.

This is equivalent to the indications for use of the product, and the information provided should be consistent with that stated in Parts IA, IB and IVA.1 of the dossier, in the Summary of Product Characteristics and on the labelling.

2. method(s) to be used for the release.

This is equivalent to the method of administration of the product, and the information provided should be consistent with that stated in Parts I and IV of the dossier, in the Summary of Product Characteristics and on the labelling.

3. Information on, and results of, previous releases of the GMOs, especially at different scales and in different ecosystems.

Possibly addressed in Part IIID, but this information is largely is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier. For example, the results of the release should include the consequences of any shedding of the virus.

4. Quantities of GMOs to be released.

Part II A. The quantities of GMO to be administered per dose should be stated.

IV. Information Relating to the Interactions Between the GMOs and the Environment.

A. Characteristics affecting survival, multiplication and dissemination.

1. biological features which affect survival, multiplication and dispersal;

Parts IIIA, IIIC 6.1, IIIC 6.2, IIIE.

2. known or predicted environmental conditions which may affect survival, multiplication and dissemination (wind, water, soil, temperature, pH etc.);

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

3. sensitivity to specific agents.

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

B. Interactions with the environment:

1. predicted habitat of the GMOs;

Part IIIE.

2. studies of the behaviour and characteristics of the GMOs and their ecological impact carried out in simulated natural environments, such as microcosms, growth rooms, greenhouses; animal houses etc may also be of relevance to medicinal products

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

3. genetic transfer capability:

(a) post-release transfer of genetic material from GMOs into organisms in affected ecosystems;

Partly covered in Part IIIC 6.2 but this information is largely required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear in detail elsewhere in the dossier.

(b) post-release transfer of genetic material from indigenous organisms to the GMOs;

Partly covered in Part IIIC 6.2 but this information is largely required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear in detail elsewhere in the dossier.

4. likelihood of post-release selection leading to the expression of unexpected and/or undesirable traits in the modified organism;

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

5. measures employed to ensure and to verify genetic stability. Description of genetic traits which may prevent or minimise dispersal of genetic material. Methods to verify genetic stability.

This entry should include detailed information specifically relevant to the environmental risk assessment and should if necessary be more extensive than that presented in Part IIC 2 of the dossier.

6. routes of biological dispersal, known or potential modes of interaction with the disseminating agent, including inhalation, ingestion, surface contact etc.

Part IIIA 1, IIIC 6.1, IIIC 6.2, IIIE.

7. description of ecosystems to which the GMOs could be disseminated.

Parts IIIA, IIIE.

C. Potential environmental impact:

1. potential for excessive population increase in the environment.

Part IIIE.

2. competitive advantage of the GMOs in relation to the unmodified recipient or parental organism(s);

Part IIIE.

3. identification and description of the target organisms;

Parts IIIA 1, IIIC 6.1, IIIE.

4. anticipated mechanism and result of interaction between the released GMOs and the target organism;

Part IIIE

5. identification and description of non-target organisms which may be affected unwittingly;

Parts IIIA1, IIIC 6.1 and IIIE.

6. likelihood of post-release shifts in biological interactions or in host range;

Part IIIE.

7. known or predicted effects on non-target organisms in the environment, impact on population levels of competitors, hosts, symbionts and pathogens;

Part IIIE.

8. known or predicted involvement in biogeochemical processes;

Part IIIE.

9. other potentially significant interactions with the environment.

Part IIIE.

V. Information on Monitoring, Control, Waste Treatment and Emergency Response Plans

A. Monitoring Techniques.

1. Methods for tracing the GMOs, and for monitoring their effects;

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

2. specificity (to identify the GMOs, and to distinguish them from the donor, recipient or, where appropriate, the parental organisms), sensitivity and reliability of the monitoring techniques;

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

3. techniques for detecting transfer of the donated genetic material to other organisms.

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

B. Control of the Release

1. Methods and procedures to avoid and/or minimise the spread of the GMOs beyond the site of the release or the designated areas of use.

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier, and is likely to be relevant in the case of vaccines disseminated as a baited formulation in an open environment.

C. Waste treatment:

1. Type of waste generated;

Parts IIIA1, IIIC6.2, IIIC6.3.

2. expected amount of waste;

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

3. possible risks;

Part IIIE.

4. description of treatment envisaged.

Part IB, but this information is largely required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

D. Emergency response plans:

1. Methods and procedures for controlling the GMOs in case of unexpected spread;

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier, and is likely to be relevant in the case of vaccines disseminated as a baited formulation in an open environment.

2. Methods for decontamination of the areas, eg. eradication of the GMOs.

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier, and is likely to be relevant in the case of vaccines disseminated as a baited formulation in an open environment.

3. plans for protecting human health and the environment in case of the occurrence of an undesirable effect.

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

Part II-H-4. The complete technical dossier supplying the information requested in Annex III of Directive 90/220/EEC, including the results of any investigations performed for the purposes of research and development.

A. The following information shall be provided:

1. Name of the product and names of the GMOs contained therein;

The information should be consistent with that provided in Part I of the dossier.

2. name of the manufacturer or distributor and his address in the Community;

The information should be consistent with that provided in Part I of the dossier.

3. specificity of the product, exact conditions of use including, when appropriate, the type of environment and/or the geographical area(s) of the Community for which the product is suited;

4. type of expected use: industry, skilled trades, consumer use by public at large etc.

In the case of medicinal products for veterinary use, any veterinary or animal care personnel, institutions etc. specified for handling the product should be stated.

B. The following information shall be provided where relevant.

1. Measures to take in case of unintended release or misuse;

Proposed measures should also appear elsewhere in the dossier as appropriate, including the Summary of Product Characteristics, the labelling and the package insert.

2. specific instructions or recommendations for storage and handling;

Proposed measures should also appear elsewhere in the dossier as appropriate including the Summary of Product Characteristics, the labelling and the package insert.

3. estimated production in and/or imports to the Community;

This information is required specifically to fulfil the requirements of the environmental risk assessment and may not necessarily appear elsewhere in the dossier.

4. proposed packaging. This must be appropriate so as to avoid unintended release of the GMOs during storage, or at a later stage;

The information should be consistent with that provided in Part I and II of the dossier.

5. proposed labelling. This must include, at least in summarised form, the information referred to in A.1, A.2, A.3, B.1 and B.2, above.

Proposed labelling and package insert particulars related to the environmental risk should appear also elsewhere in the dossier (ie., Part I) as appropriate, should be consistent with the Summary of Product Characteristics and should comply with the requirements of Council Directive 81/852/EEC.

Part II-H -5. The environmental risk assessment resulting from the information provided under points II-H-1 to II-H-4 above.

The assessment of environmental risk should follow logically from the data presented in II-H-1 to II-H-4. Risks to human health, non-target animals, soil, water, air, individual ecosystems etc. should be addressed as appropriate. This section should be compiled in accordance with the Note for Guidance III/5573/94 on Environmental Risk Assessments for Veterinary Medicinal Products Containing or Consisting of GMOs.

Part II-H-6. Conclusion.

The applicant should present his overall conclusions.

5. PRESENTATION OF PARTICULARS IN THE EXPERT REPORTS

Part II-H of the main documentation should be addressed in the Analytical (Chemical, Pharmaceutical and Biological or Microbiological) Expert Report and should include a critical evaluation, the opinion of the expert as to whether sufficient guarantees have been provided as to the suitability of the product for its proposed use, and an appendix containing a summary of all the important data.

The entries should be compiled by the Expert in accordance with the general requirements for Expert Reports outlined in the Notice to Applicants. In particular, the expert should be appropriately qualified.

Guideline for the conduct of the environmental risk assessment for veterinary medicinal products which contain or consist of genetically modified organisms

1. BACKGROUND AND INTRODUCTION

This guidance concerns the environmental risk assessment needed to comply with the requirements of Article 28(2) of Council Regulation 2309/93 on the licensing of veterinary medicinal products which contain or consist of genetically modified organisms (GMOs) . The Regulation makes provision for an environmental risk assessment similar to that in Directive 90/220/EEC on the Deliberate Release into the Environment of Genetically Modified Organisms (GMOs). In both this Directive and in the Regulation, the environmental risk assessment is derived from the technical dossier containing the information required under Annex II and III of the Directive. Under Council Regulation 2309/93 therefore, the environmental risk assessment should be a reasoned statement of the overall risk of damage to human health and to the environment from the proposed marketing of a veterinary medicinal product containing or consisting of a GMO.

There are no hard and fast rules for risk assessments. The following guidance outlines the generally accepted terminology for a risk assessment and includes some practical steps and a workable format to aid applicants.

The level of detail to be considered in a risk assessment will depend on circumstances. It will be lower, for example, where it is immediately obvious that the hazards and hence the consequent risks are low or that the proposed control measures are clearly adequate to limit the contact of the product with humans and the environment.

2. SCOPE OF THE REGULATION (Types of products)

This guidance has been based largely on the considerations appropriate to what will probably be the most likely type of veterinary medicinal products containing or consisting of GMOs capable of replication or of transferring genetic material, namely, live viral, bacterial or parasitic vaccines including vector vaccines.

3. ENVIRONMENTAL RISK ASSESSMENT

3.1 General considerations

For veterinary medicinal products it may be appropriate first to consider the risks to human health and to address whether it is necessary to take certain measures to control the risks arising from the administration and use of the product. The potential risks to the environment should then be assessed on the basis that those control measures are in place.

The main considerations for the risks to human health will be determined by whether or not the GMO is a zoonotic agent, or likely to be a zoonotic agent taking into account the characteristics of the parental organism, any organisms used as donors and the possibility of changes in host range, pathogenicity or tropism as a result of the genetic modifications. The classification system for pathogenicity of micro-organisms as set out in Council Directive 90/679/EEC, as amended, may provide a useful reference for these considerations.

To all intents and purposes, the human health part of the environmental risk assessment considers the risk to human health as if humans were a sub-set of the wider environment, or another non-target species. The human risk assessment must include consideration of the risk to those who handle or administer the product and or treated animals, risks to relatives and other contacts of these operators and risk to the general public. It will be necessary to consider the possible effects on healthy humans as well as to more vulnerable individuals (the young or old, immunocompromised or otherwise susceptible). For example, the increasing incidence of people who are receiving immunosuppressants, or have recently undergone chemotherapy, or who have developed AIDS may mean that there is a section of the population who are at greater risk and this needs to be taken into account at each stage of the risk assessment.

3.2 Sources of information

The risk assessment is intended to be an overall statement reflecting all the information contained in the dossier.

Although wherever possible the risk assessment should be based on quantifiable outcomes, it is recognised that many of the judgements must necessarily be qualitative. But any statements or assertions in the assessment should be supported by some evidence, quantitative where possible.

How much information is needed on any particular point will depend on its importance in the assessment and the extent to which it is generally accepted material. There is no need to spell out in great detail what is elsewhere in the dossier or in text books or literature. But the logic of the argument should be clear and enough justification should be included on any unusual or particularly important points for the assessment to be testable. Note that it is always permissible to assume the worst and act accordingly, if the cost of gathering the information (by experimentation or review) for a more precise assessment is disproportionate.

4. FRAMEWORK FOR RISK ASSESSMENT

The aim of the risk assessment is to identify hazards, to estimate the likelihood that the hazards will lead to actual harm and to take decisions regarding the appropriate control measures. The main elements of a risk assessment are therefore:

i. hazard identification;

ii. assessment of the likelihood that the hazard will occur;

iii. assessment of exposure to the hazard and the consequences of that exposure;

iv. assessment of the level of risk (by consideration of the severity of any adverse consequences and the likelihood that they will occur);

v. selection and assignment of appropriate control measures (risk management).

4.1 Assessment of risk to humans

4.1.1. Hazard identification

In the context of this guidance, hazards are defined as those features of the GMO which have the potential to cause harm, either directly (such as infection) or through some form of possible event (such as the transfer of hazardous genes to and from other organisms). It is important to be exhaustive in the identification of possible hazards and not to discount at this stage any of the hazards given below on the basis that they are unlikely to occur. The assessment of possible exposure and likelihood are separate stages of the assessment process.

The stage of the assessment should aim to identify all possible adverse effects on humans and should include the following:

4.1.1.a. Pathogenicity or other adverse effects
With respect to humans and animals, details of the pathogenicity of the parental organism and the GMO itself, will have been considered during the safety studies on the product. When determining the hazards associated with the GMO, consideration should be given to the pathogenicity and virulence, any changes to the host range or tissue tropism and, if it is still potentially pathogenic, whether the GMO is susceptible to available therapies or is expected to exhibit altered interactions with host defence mechanisms. As well as the possibility of infection in healthy individuals, the possibility of infection in immunocompromised or other especially susceptible individuals should be identified.

4.1.1.b. Genetic instability (especially attenuating mutations)
Consider whether the GMO is stable over repeated generations, and in particular, whether any genetic instability could affect attenuating mutations or alter the behaviour of the GMO, particularly if it could result in a reversion to virulence. The type of attenuating mutation (point mutation or deletion) will be an important consideration in assessing the likelihood of the hazard ocurring. Attention should be paid to those bacterial GMOs if

potentially transferable vectors based on plasmids, bacteriophages or transposons have been used.

4.1.1.c. Gene transfer

Gene transfer may be considered a hazard under some circumstances, for example if it could result in the spread of genes to other organisms with potentially undesirable consequences. In some senses it can be considered as a subset of genetic stability.

4.1.1.d. Survival / dissemination

The ability of the GMO to survive for long periods in the environment (for example in the litter of the poultry house or grazing pastures) may constitute a hazard under some circumstances, for example if it could mean that there is a greater likelihood of contact with individuals. This may be further compounded if survival offers an increased possibility of wide spread dissemination by water or other routes or by any arthropod or animal vectors.

4.1.2. Assessment of the degree of exposure and the likelihood of the hazard occurring

In order to determine the risk posed by the GMO it will be necessary to determine the likelihood of any of the above hazards occurring i.e. whether people will be exposed to the hazard associated with a GMO and, if so, whether they would suffer an adverse effect.

4.1.2.a. Potential for exposure to the GMO in the product

At this stage, it will also be necessary to consider whether everyone exposed to the GMO would suffer an adverse effect or whether any adverse effect would occur only in a small

proportion of exposed individuals. Infrequent adverse effects may be either due to a low probability of an effect occurring in any given individual or because a small proportion of the population is susceptible. The latter may include immunocompromised individuals or those with a particular vaccination status or on an antibiotic regimen.

One important component of this factor is whether the wider environment (including other humans) comes into contact with the GMO in the product under normal circumstances (i.e. are exposed to the GMO). The degree of exposure of operators will have a bearing on the likelihood of a hazard occurring. When considering the degree of exposure of operators and their relatives and contacts and the general public to the product, the following matters should be taken into account.

4.1.2.a (i) Type of packaging and procedures before and after administration

Most, if not all, veterinary medicinal products containing GMOs will be securely packaged on receipt and the packaging should allow any initial preparatory steps (e.g. reconstituting freeze-dried preparations) to be undertaken in a safe and aseptic manner. However, the proposed method of preparation and administration will have a bearing on the degree of

posure of operators to the GMOs and need to be considered. For example, single dose preparations for administration to a companion animal in the surgery is likely to result in less exposure than mass medication of farm animals. It may be appropriate to consider who is likely to administer the product (veterinary surgeon or farmer) and the likelihood of any necessary instructions for safe use of products being achievable. It will also be necessary to consider whether or not unused product can be readily disposed of in a reliably safe manner.

4.1.2.a (ii) Route of administration (parenteral vs. oral vs. oculonasal vs. spray)
It may be expected that there is more opportunity for exposure of the operator to the product organisms when the product is administered by spray, orally or oculonasally than by injection but the risks of self injection must be borne in mind.

4.1.2.a.(iii) Shedding of live product organisms (route, numbers, duration)
The extent to which the product organisms multiply in the host, can be excreted and spread will have been studied as part of the safety studies. Many products may well consist of attenuated or replication defective organisms and the likelihood of exposure will be less than that associated with the wild type, parental strain.

The overall degree of exposure of humans such as animal attendants should be indicated. It should be noted that high exposure does not necessarily mean high risk and conversely that even 'low' exposure, but with severe consequences, may lead to an unacceptable risk.

It is recommended that the possibility of exposure and likelihood of hazards occurring is qualitatively judged as either 'negligible', 'low', 'moderate' or 'high'.

4.1.3. Assessment of level of risk

Having identified any hazards and assessed the degree and likelihood of exposure and the consequences of that exposure it is necessary to evaluate the risk associated with each hazard. Risk is generally held to be the product of exposure/likelihood and consequence. It is inevitably always going to be difficult to 'multiply' qualitative statements such as 'high' and 'low', but table 1 should help this process. The risk matrix is not definitive and there will always be some scope for flexible, case by case evaluation. In many cases, it will be necessary to decide between one of two outcomes and as in the earlier parts of the process, some justification for the choice should be provided. In addition, a range of risks may be apparent if more than one hazard is being evaluated. There will therefore be a need to make an overall assessment of the risk taking all factors into consideration.

Once an overall assessment of the risk associated with each hazard has been produced it will be necessary to evaluate the significance of the risk.

It is generally considered that any risk other than 'effectively zero' or 'low' is unacceptable without some consideration of measures and proposals to control the risks to human health.

4.1.4. Consequences of a hazard occurring

This stage of the assessment should consider, for each identified hazard, what is the result of the hazard occurring i.e. what effect it may have on an exposed individual or population. It is anticipated that the range of consequences will fall between those that are negligible and self-limiting and those that would be severe, either having an immediate and serious effect or possibly leading to long term, harmful consequences.

It is suggested that the consequences of each hazard is indicated qualitatively as 'negligible', 'low', 'medium' or 'severe'.

An adverse effect may be either immediate or delayed. Immediate and relatively trivial effects such as seroconversion in casual contacts may be extremely easy to identify but may not be particularly important. However, longer term and less obvious effects, such as oncogenicity or toxicity will clearly be difficult to assess but extremely important.

The assessment of the consequences of a hazard occurring will need to consider the effects on individuals as well as the overall community. For each hazard it may be necessary to split the considerations into the 'worst case' and the 'normal case'. During the overall assessment of the level of risk, such differences should then be weighed up in arriving at the final risk assessment. For example, the consequences to rare individuals may be judged to be 'serious'. However, because such individuals do not form a large part of the community (and therefore the likelihood of the hazard occurring is low), the risk associated with the particular hazard may be acceptable.

4.1.5. Control of risk

This stage of the risk assessment will require some consideration of the particular aspect of the assessment which lead to an unacceptable level of risk. For example, if it were caused by a lack of detailed knowledge on a particular hazard then it might be necessary to acquire further information, either by experimentation or from published literature. Alternatively, it could be that changes to the instructions for use or to any recommended precautions would reduce the level of exposure to staff or other people. In any case, personnel, such as those administering the product and those handling the animals at the time, will be subject to worker protection legislation such as the Biological Agents Directive (90/679/EEC as amended by 93/88/EEC), requiring among other things, risk assessment and appropriate control measures.

4.2 Assessment of the risks to the environment

Having decided on the controls (if any) that are appropriate in order to minimise the risks to humans, it is necessary to evaluate whether there could be any adverse effect on the environment resulting from the use of the product. The characteristics of the GMO need to be considered, particularly its host range and pathogenicity. Account must be taken of the characteristics of the parental organism, any organisms used as donors and the

possibility of changes to host range, pathogenicity or tropism as a result of the genetic modifications.

The objective of the environmental part of the risk assessment is to determine the probability of adverse consequences, or 'harm', to the environment. Harm results if hazards are realised. The steps are in principle as for the human health part of the risk assessment, but the particular considerations are of course different.

4.2.1. Hazard identification

The starting point for risk assessment is to identify the characteristics of the GMO which are a hazard because they have the potential to cause harm in the receiving environment. Appropriate information about the recipient or parental organism and the donors as well as information about the GMO itself, should be considered.

4.2.1.a. Capacity to transmit to non-target species
The specificity of the host range is very important for veterinary products. Any likely changes as a result of the genetic modification should be taken into account.

4.2.1.b. Shedding of live product organisms (route, numbers, duration)
The extent to which the product organisms multiply in the host, can be excreted and spread will have been studied as part of the safety studies. Many products may well consist of attenuated or replication defective organisms and the likelihood of exposure will be less than that associated with the wild type, parental strain. However, the potential for organisms passaged from animal to animal to become less attenuated must be taken into consideration.

4.2.1.c. Capacity to survive, establish and disseminate
This is also a key consideration: if an organism is not capable of surviving, say, because of multiple disablement, then other hazards are likely to be minimised. The risk assessment could be completed at this stage if the risks to the environment are low or effectively zero. However, if it is likely that the organism could survive for a sufficiently long period for it to cause harm, and possibly establish and disseminate in the environment, then not only this hazard but also other hazardous characteristics need to be considered.

4.2.1.d. Potential for gene transfer
Although most organisms have the ability to transfer genes, some do not. Consider, in particular, the extent to which the method of modification might increase the potential for transfer, as, for example, in the case of non-integrating viral vectors.

4.2.1.e. Products of expression of inserted sequences
Identify all products of gene expression that could cause harm, bearing in mind that an inserted gene might code for a product that is toxic, or otherwise detrimental, to other organisms. Consider the extent to which those products could have an effect on other organisms.

4.2.1.f. Phenotypic and genotypic stability
Consider whether genes inserted into the GMO on extrachromosomal elements might be transferred more readily and the extent to which genotypic instability might lead to phenotypic instability.

4.2.1.g. Pathogenicity to other organisms

The pathogenic properties of many organisms used as recipient or parental organisms are well documented; these should be identified, if appropriate. Consider whether a change in host range could occur as a result of the genetic modification which has been undertaken.

4.2.1.h. Potential for other effects

Consider whether the GMO might have the potential to exert other effects such as the transmission and replication of viruses in other organisms as a result of transcapsidation, and the effects of recombination.

4.2.2. Assessment of likelihood

The next step is to estimate the likelihood (probability and frequency) of hazard(s) being manifested. A key factor in determining this is the potential receiving environment. This includes the wider as well as the local environment in which the product is intended or likely to be used.

Particular characteristics of the local environment that could contribute to manifestation of the hazard should be identified and assessed. Climatic, geographical and soil conditions, demographic considerations, the types of flora and fauna in the potential receiving environment are some of the important ones.

Consideration should be given to any potential exposure of the living and non-living environment to the GMOs and the magnitude and duration of such exposure.

When estimating probabilities and frequencies, consideration should include the number of organisms that might reach the environment since the probability that a hazard will be realised will often be influenced by the number of viable organisms in the environment due, for example, to excretion. For the hazard 'survival capacity', therefore, it is appropriate to assess the proportion of the GMOs that are likely to survive. In the case of the likelihood of gene transfer, the probable number of such events or the extent to which transfer will occur should be considered. If the GMO has pathogenic characteristics, assess the proportion of target organisms in the environment likely to be affected, including taking into consideration, the likelihood of the GMO to spread to or reach these organisms.

The mode of administration might have an impact on the likelihood that hazard(s) will be manifested. For example, spray or other forms of mass administration are more likely to lead to the introduction of the GMO into the environment than if given by injection.

Likelihood should be expressed as 'high', 'medium', 'low' or negligible'.

4.2.3. Assessment of level of risk

Having judged the magnitude of harm if the hazard were to be realised, and the likelihood or frequency of such harm being caused, the level of risk is assessed by considering the combined effect of these two components.

This should be carried out for each of the hazards identified. The matrix in Annex 1 used for the human health part of the risk assessment can be used again to come to an evaluation of the environmental risk for each environmental hazard.

4.2.4. Assessment of the consequence

For each hazard of the GMO identified, whenever it is possible or probable that the GMO in the product will reach the environment, it must be considered whether that environment would cause or allow the hazard to be realised. Thus, again, the characteristics of the potential receiving environment need to be considered.

An assessment of the magnitude of harm is based on the assumption that the hazard will be realised. Inevitably there will be a degree of judgement in making the assessment, but the consequences should be described as 'severe', 'medium', 'low', or 'negligible'. A 'severe' consequence might be a major change in the numbers of one or more species leading to negative effects on the functioning of the ecosystem and/or other connected ecosystems. It is unlikely that the changes would be reversible. A 'low' consequence might be if any change in population densities is such that it has no negative effects on ecosystem function and no impact on endangered or beneficial species.

The above illustrations reflect the potential effect of the GMO on populations. In some cases, however, it may be more appropriate to consider the likely effects on individual organisms, for example endangered mammals. In most cases it should be possible to use the guidelines to assess in qualitative terms the degree of harm which a particular GMO might cause.

4.2.5. Selection and assignment of appropriate control measures (risk management)

If the environmental risks are not as low as reasonably practicable, the process of risk assessment in relation to that hazard should be repeated to ascertain whether the application of additional management techniques could reduce the level of risk. Consideration might be given, for example, to limiting the proposed routes of administration to those likely to lead to a lower level of risk.

5. SUGGESTED FORMAT FOR PRESENTATION OF CONCLUSIONS OF RISK ASSESSMENT

Applicants may find the following structure useful to record their risk assessment.

1. Summary
Summary of the overall risk of damage to the environment (including human health) from the proposed marketing of the GMOs forming the subject of the application.

2. Assessment of risk to humans

2.1. Hazard identification: Hazardous characteristics of the GMO that could, in certain circumstances, lead to harm in humans :

a. Pathogenicity or other adverse effects

b. Genetic instability (especially attenuating mutations)

c. Gene transfer

d. Survival / dissemination

2.2. Assessment of the degree of exposure and the likelihood of each hazard occurring

2.3. Assessment of level of risk

2.4. Consequences of a hazard occurring

2.5. Assessment of the overall risk of harm to humans (the total risk after consideration of the risk of each of the hazards occurring): High, medium, low, effectively zero.

3. Assessment of the risks to the environment

3.1. Hazard identification Hazardous characteristics of the GMO that could, in certain circumstances, lead to harm to the environment

a. Capacity to transmit to non-target species

b. Shedding of live product organisms (route, numbers, duration)

c. Capacity to survive, establish and disseminate

d. Potential for gene transfer

e. Products of expression of inserted sequences

f. Phenotypic and genotypic stability

g. Pathogenicity to other organisms

h. Potential for other effects

3.2. Assessment of likelihood

3.3. Assessment of level of risk

3.4. Assessment of the consequence

3.5. Assessment of the overall risk to the environment (the total risk after consideration of the risk of each of the hazards occurring): High, medium, low, effectively zero.

4. Assessment of the overall risk

Assessment of the overall risk to humans and the environment (from Points 2.5 and 3.5 above) .

Table I

ESTIMATION OF RISK

Consequence of Hazard	**Likelihood of Hazard**			
	High	Moderate	Low	Negligible
Severe	High	High	Medium	Effectively Zero
Medium	High	High	Medium/Low	Effectively Zero
Low	Medium/Low	Low	Low	Effectively Zero
Negligible	Effectively Zero	Effectively Zero	Effectively Zero	Effectively Zero

This matrix is not intended to be definitive, but illustrative of the way in which an estimate of risk might be obtained from the consequence and likelihood that a hazard will be realised. Different components may be differently weighted, however, depending on the knowledge and experience of the GMO and operation involved.

Guidance on the integration of the evaluation of the environmental risk assessment with the evaluation of the rest of the application for marketing authorisation for a medicinal product consisting of or containing live genetically modified organisms

1. INTRODUCTION

From 1 January 1995, applications for marketing authorisations for medicinal products which contain or consist of live genetically modified organisms will fall within the scope of Council Regulation 2309/93. The particulars and documents required in support of an application for marketing authorisation for such a medicinal product will include an environmental risk assessment and related information, in accordance with Articles 6.2 or 28.2 of the Regulation (depending on whether it is for human or veterinary use).

The authorisation procedure, which is laid down in the Regulation, will be mandatory for such medicinal products containing live GMOs, since they fall within the scope of the annex, part A. The evaluation of the entire dossier, which must take place according to a strict time-table, will be coordinated by a rapporteur appointed by the CPMP/CVMP.

The key principles in the evaluation procedure of a medicinal product containing a live GMO are as follows:

2. APPLICATION DOSSIER

A single application dossier will be submitted to the European Medicines Evaluation Agency (EMEA). (The number of copies and languages will be set out in the Notice to Applicants).

In the case of a medicinal product consisting of or containing a live GMO, the dossier will include (Articles 6.2 and 28.2 of the Regulation):

- a copy of written consents issued by the competent authorities to the deliberate release of GMOs for research and development purposes,
- the results of any investigations performed for the purposes of research and development
- the complete technical dossier supplying the information as set out in Annexes IIA and III of 90/220/EEC,
- the environmental risk assessment resulting from this information

3. PRESUBMISSION

An applicant may seek advice from the Agency within its Committees on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products. Usually the Committee concerned will appoint one of its members to coordinate the advice to be given. Advice may also be sought on the fulfillment of the requirements of Article 6.2 or 28.2 of Regulation N° (EEC) 2309/93. Applicants may seek advice on applications prior to submission. See appropriate section in the Notice to Applicants on advising applicants on the conduct of various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products. (Article 51 of the Regulation)

4. AUTHORISATION PROCEDURE

In accordance with Article 53 of the Regulation at the start of the procedure, the CPMP/CVMP shall appoint a rapporteur to coordinate the evaluation

During the evaluation the rapporteur shall in a timely manner hold the necessary consultations with the bodies set up in accordance with 90/220/EEC. In the first instance, it is recommended that the rapporteur contact one of the Competent Authorities for 90/220/EEC which will then coordinate the views of the other Competent Authorities. The conclusions and results of any consultations will be included in the assessment report, including requests for clarification or further information.

The CPMP/CVMP will give its opinion within 210 days of the receipt of a valid application. The opinion shall respect the environmental safety requirements resulting from the risk assessment on the basis of Directive 90/220/EEC to ensure that appropriate measures are taken to avoid the adverse effects on human health and the environment which might arise from the deliberate release or placing on the market of a medicinal product containing live GMOs.

Scientific Evaluation	**Timing**
Committee receives the valid application, a rapporteur (taking into consideration any proposal from the applicant for the choice of a rapporteur) and as appropriate a co-rapporteur, is nominated along with the experts in the evaluation team; necessary consultations with the bodies set up in accordance with 90/220/EEC to take place during this period. Requests for further information/ clarification which relate to the environmental risk assessment, to be proposed during this time. The secretariat liaises with the applicant, informing them of the rapporteur (and co-rapporteur) and timetable which has been prepared.	Day 1
Rapporteur (and co-rapporteur, as appropriate) circulate their preliminary assessment reports to the Committee. This will include the evaluation of the information presented in accordance with article 6.2 or 28.2 of Regulation N°2309/93 and the conclusions and results of consultations with the bodies set up in accordance with Directive 90/220/EEC. Only one assessment report of the ERA would be prepared for this evaluation.	Day 90
Committee considers preliminary assessment report(s) and establishes those issues which the applicant is invited to clarify and the clock is stopped	Day 120
Applicant submits a written response to the Agency Clock restarts when a response to all parts of the dossier is received	Day 120
Rapporteur(/co-rapporteur) prepares a report with conclusions on the written response of the applicant and circulates to members and the applicant	Day 150
The need for an oral explanation with the Committee is discussed with the rapporteur, which is then arranged by the secretariat if necessary (clock may be stopped to allow the applicant to prepare the oral explanation)	Day 180
The Committee members conclude the evaluation and adopt the opinion	Day 210

CHAPTER VII

ADDITIONAL INFORMATION

STANDARD FORMAT FOR APPLICATIONS FOR AUTHORISATION FOR NON-IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS
(NATIONAL AND COMMUNITY PROCEDURES) [1]

PART I SUMMARY OF THE DOSSIER

- I.A Administrative data
- I.B Summary of product characteristics
- I.C Expert reports on:
  - chemical, pharmaceutical and biological documentation
  - safety documentation
  - residues documentation (if necessary)
  - pre-clinical and clinical documentation

PART II CHEMICAL PHARMACEUTICAL AND BIOLOGICAL DOCUMENTATION

- II.A Composition
- II.B Method of preparation
- II.C Control of starting materials
- II.D Control tests on intermediate products
- II.E Control tests on the finished product
- II.F Stability
- II.Q Other information

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[1] Each application must contain a detailed index, with volume and page number of the file clearly indicated for each item

PART II Bis CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL DOCUMENTATION FOR VETERINARY MEDICINAL PRODUCTS DERIVED FROM BIOTECHNOLOGY

- II Bis A Composition
- II Bis B Method of preparation
- II Bis C Production and control of starting materials
- II Bis D Control tests on intermediate products
- II Bis E Control tests on the finished product
- II Bis F Stability
- II Bis Q Other information

PART III SAFETY AND RESIDUES DOCUMENTATION

III.A Safety Documentation

- A.1 Precise identification of the substance concerned by the application
- A.2 Relevant pharmacological studies
- A.3 Toxicological studies
- A.4 Studies of other effects
- A.5 Ecotoxicity

Conclusions

III.B Residue Documentation

- B.1 Precise identification of the product concerned by the application
- B.2 Residue studies
- B.3 Routine analytical method for the detection of residues

Conclusions

PART IV PRE-CLINICAL AND CLINICAL DOCUMENTATION

IV.1 Pre-clinical documentation

- 1.A Pharmacology
- 1.B Tolerance in the target species
- 1.C Resistance

IV.2 Clinical documentation

STANDARD FORMAT FOR APPLICATIONS FOR AUTHORISATION FOR IMMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS
(NATIONAL AND COMMUNITY PROCEDURES)

PART I SUMMARY OF THE DOSSIER

- I.A Administrative data
- I.B Summary of product characteristics
- I.C Expert reports on:
  - analytical (physico-chemical, biological and microbiological documentation)
  - safety documentation
  - efficacy documentation

PART II CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL DOCUMENTATION

- II.A Qualitative and quantitative composition of the constituents
- II.B Description of the method of preparation of the finished product
- II.C Production and control of starting materials
- II.D Control tests during production
- II.E Control tests on the finished product
- II.F Stability
- II.Q Other information

PART III SAFETY DOCUMENTATION

PART IV EFFICACY DOCUMENTATION

PART V GENERAL CONCLUSIONS

BIBLIOGRAPHICAL REFERENCES

EC APPLICATION FORMAT (Part IA)

This is not intended to be a "formulaire", or for completion as an "application form". It is a list of headings, in sequence, to facilitate examination of dossiers and ensure all relevant data is included. Where insufficient space is provided on the form, full details should be provided separately, following the same order as in the form.

Part IA - Administrative data

Part IA:

Fees, declaration and signature

It is hereby confirmed that fees are going to be paid/have been paid according to the national rules.

(If fees have been paid, please attach proof of payment)

It is hereby confirmed that all existing data which are relevant to the benefit/risk assessment of this veterinary medicinal product have been supplied in the dossier Parts II, III and IV.

Place, date _____

(Function and signature(s) of the applicant)

Part 1A:

Type of Application

Processing number.....
(for competent authority use only).....

1. This application concerns:

O A national application (if available, number: .....)

O An application according to Art. 17 of Directive 81/851/EEC as amended (mutual recognition procedure)

Reference Member State: .....
date of authorisation: .....
marketing authorisation number: .....
EC Member States involved in the mutual recognition procedure:
EC Member States where additional national applications are pending: .....
Non EC/EEA States where additional national applications are pending: .....

If there are differences between the pending national application and the decentralised procedure, elaborate:

☐ different indications

☐ different dossier Part II

☐ different dossier Part III

☐ different dossier Part IV

O An EC-application according to Council Regulation EEC No. 2309/93 (centralised procedure)

rapporteur: ..... co-rapporteur:.....

O Part A O Part B

date of acceptance as a Part B veterinary medicinal product by the CVMP: .....

O A resubmission (previous national application number): .....

O A renewal (i.e. updated Part 1A) of a marketing authorisation granted under Directive 87/22/EEC (concertation no .....)

2. <u>The application is in accordance with the following legal base</u>:

O A full application (a full dossier)
O An abridged application
  O according to Directive 81/851/EEC Article 5.10a)i)
  (A letter of consent from the holder of the authorisation of the original veterinary medicinal product should be included.)
  O according to Directive 81/851/EEC Article 5.10a)ii)
  O according to Directive 81/851/EEC Article 5.10a)iii)
  (Proof should be provided that an essentially similar product has been authorised within the Community, in accordance with Community provisions in force, for not less than six/ten years and is marketed in the Member State for which the application is made.)

O Other abridged application (extension):
  ☐ quantitative change in declared active substance/different strength
  ☐ qualitative changes in declared active substance(s) including addition or deletion
  ☐ addition of an indication to a different therapeutic area
  ☐ change of an indication to a different therapeutic area
  ☐ different route of administration
  ☐ different pharmaceutical form
  ☐ change of bioavailability
  ☐ change of pharmacokinetics
  ☐ addition or change of target animal species
  ☐ shortening of the withdrawal period for a veterinary medicinal product used in food-producing animals

O Biological substances or products of biotechnology:
  ☐ replacement with one of a different molecular structure
  ☐ modification of vector including master cell bank from different source

O Other abridged applications not listed above, please specify

3. This is an application for:

- ☐ An "essentially similar" product
- ☐ A veterinary medicinal product containing a new active substance
- ☐ A veterinary medicinal product containing an excipient not previously authorised in a veterinary medicinal product
- ☐ A veterinary medicinal product containing a new combination of known active substances
- ☐ A veterinary medicinal product with a new proposed indication
- ☐ A new strength of an authorised veterinary medicinal product
- ☐ A new pharmaceutical form of an authorised veterinary medicinal product

When a veterinary medicinal product is intended for use in food-producing animals

- ☐ Maximum Residue Limits according to Council Regulation 2377/90/EEC are published in the Official Journal of the European Communities

Substance:	Date of publication:	Species:
.....	.....	.....

- ☐ Maximum Residue Limits according to Council Regulation 2377/90/EEC are applied for:

Substance:	Date of submission:	Species:
.....	.....	.....

1.	Proposed brand name of the veterinary medicinal product in the Community/concerned Member State: If different brand names[2] in different Member States are proposed in a mutual recognition procedure, these should be listed: Country: Name:
1.1	Name of the active ingredient(s) (INN, Ph. Eur., National Pharmacopoeia, trivial name and chemical description):
1.2	Pharmacotherapeutic classification (use ATC vet classification):
1.3	Target species
2.	Pharmaceutical form and strength (Please use CVMP List of Allowed Terms):
2.1	Route of administration (Please use CVMP List of Allowed Terms):
2.2	Container, closure and administration devices (Please use CVMP List of Allowed Terms):

[2] A justification for different brand names should be appended in an Annex (see Chapter I and item 7.2 of this format).

2.2.1	Package sizes
2.2.2	Shelf life
2.2.3	Shelf life (after first opening of container)
2.2.4	Shelf life (after reconstitution)
2.2.5	Storage conditions

2.3 Dispensing/classification proposed by the applicant:

Veterinary medicinal products
- O subject to prescription
- O subject to other controls (specify)
- O not subject to other controls

2.4.1 For veterinary medicinal products subject to prescription[3]:

- O Veterinary medicinal products on prescription which may be renewed
- O Veterinary medicinal products on prescription which may not be renewed
- O Veterinary medicinal products on special prescription
- O Veterinary medicinal products on restricted prescription

2.4.2 For veterinary medicinal products not subject to prescription:

- O Promotion to health care professionals only
- O Promotion to the general public

2.4.3 *(Only applications submitted to Germany, Ireland, the Netherlands, Sweden & the U.K):*

- O Supply through pharmacies only
- O Supply through non-pharmacy outlets

Applications submitted to the UK only:

- O Pharmacy
- O Pharmacy merchant list
- O General sale list

[3] Not all the listed options are applicable in each Member State. Applicants are invited to indicate which categories they are requesting, however, the Member States reserve the right to apply only those categories provided for in their national legislation.

3.	Applicant (= future marketing authorization holder/future person responsible for placing the veterinary medicinal product on the market): Name: Address: Country: Telephone: Telefax:
3.1	Person responsible for the technical data of the dossier (Spain & Portugal): Name: Address: Country: Telephone: Telefax:
3.2	The following person is authorised for communication on behalf of the applicant during the procedure: Person of contact: Address: Country: Telephone: Telefax:
3.3	Address for regulatory communication between the marketing authorisation holder and competent authorities after authorisation, if different from 3.2: Name: Address: Country: Telephone: Telefax:

3.4 Manufacturer(s) of the finished veterinary medicinal product and sites of manufacture (including a description of the steps they perform and the location of qualified person) Name: Address: Country: Telephone: Telefax:
3.5 The manufacturer/importer responsible for batch control in the EEA: Name: Address: Country: Telephone: Telefax:
3.5.1 Site where batch control takes place: Name: Address: Country: Telephone: Telefax:
3.6 Manufacturer(s) of the active substance(s): Name: Address: Country: Telephone: Telefax: Drug Master File reference/E.P. certificate of suitability reference number, if applicable: Date of submission:

3.7 Contract companies used for bioavailability or bioequivalence trials: For each contract company, give: Name: Address: Country: Telephone: Telefax: Task performed according to contract:
4. Qualitative and quantitative composition in terms of the active substance(s) and the excipient(s): A note should be given to which quantity the composition refers to (e.g. 1 capsule) List the active substance(s) separately from the constituents of the excipients

4.1 Non-immunological medicinal product

Name of the	**Quantity**	**Unit**	**Reference standards**
- active substances:			
1.			
2.			
3. etc.			
- excipients:-			
1.			
2.			
3. etc.			

Details of any overages: - these should not be included in the Formulation Columns but stated in this section.
- active substance(s)
- excipient(s)

4.2 Immunological veterinary medicinal product

Names of ingredients[4]	**Quantity**[5] **/dose or /ml**	**Function**	**Reference to standards**
Active ingredients			
Constituents of the adjuvant			
Constituents of the excipients[6]			
Constituents of the diluent			
Constituents of the pharmaceutical form			

4 See Part 6, A.2 of the Annex to the Directive.

5 See Part 6, A.3 of the Annex to the Directive.

6 For the purposes of this section, excipients mean products other than the active ingredient and the adjuvant, blended to prepare the finished product.

Marketing Authorisation particulars

5. Marketing applications for this veterinary medicinal product in the EEA (i.e. from the same company or a related company, i.e. "daughter", "sister" or "mother" company of the same corporation/holding company or licensee, containing the same active substances for a comparable indication)	
Authorised:	country: date of authorisation: authorization number: trade name:
Pending:	country: date of submission: application number
Rejected:	country date of rejection application number
Withdrawn: (by applicant before authorisation)	country date of withdrawal application number trade name reason for withdrawal
Withdrawn: (by applicant after authorisation)	country date of withdrawal application number trade name reason for withdrawal
Suspended/revoked/ withdrawn (by competent authority)	country date of suspension: authorization number: reason for withdrawal: trade name

6. For new active substances, marketing authorisations outside the EEA (i.e. from the same company or a related company, i.e. "daughter", "sister" or "mother" company of the same corporation/holding company or licensee, containing the same active substances for a comparable indication)	
Authorised:	country: date of authorisation: authorisation number: trade name:
Pending:	country: date of submission: application number
Rejected:	country date of rejection application number
Withdrawn: (by applicant before authorisation)	country date of withdrawal application number trade name reason for withdrawal
Withdrawn: (by applicant after authorisation)	country date of withdrawal application number trade name reason for withdrawal
Suspended/revoked/ withdrawn (by competent authority)	country date of suspension: authorization number: reason for withdrawal: trade name

7.	Appended Documents
7.1	Manufacturer's Authorisations required under 81/851/EEC Article 24 (or equivalent, if outside the EEA)
7.2	Justification of use of one or more trade name in the Member States, if appropriate
7.3	List of samples sent with the application

Instructions for completion of Section 4 of the application format:

- Enter the constituent(s) as the actual substances included in the formulation (e.g. as salt or hydrate) and then as the active entity equivalent where appropriate.
- A specification should always refer to the latest published official monograph. Where an ingredient has no official monograph please enter company standard. Official abbreviations should be used for pharmacopoeias.
- Expression of quantity of active substance:
  a) For pharmaceutical forms that comprise a defined dosage unit, the quantity should be expressed per unit (ampoules, capsules, coated tablets, prefilled syringes, suppositories, single-use vials etc.).
  b) For pharmaceutical forms that do not comprise a defined dosage unit, the quantity should be expressed by weight, by volume or by unit.
- Recommended abbreviations for quantities:
  a) Quantities expressed as mass:

     g - gram; mg -milligram; µg - microgram; ng - nanogram
  b) Quantities expressed as volumes:

     ml - millilitre; µl - microlitre ; nl - nanolitre
  c) Quantities expressed as amount of substance e.g. for inorganic salts in large volume parenterals:

     mol - mole; mmol - millimole; µmol - micromole
  d) Quantities expressed as Units:

     U - Units; kU - kiloUnits; MU - MegaUnits
  e) Quantities expressed as units of radiation:

     MBq - Megabecquerels; GBq - Gigabecquerels
  f) Adjustable quantities:

     Insert upper and lower limit
- Trailing zeros following the decimal point may be omitted e.g. 10.02 mg will suffice.
- Include head-space gases used in ampoules etc. and propellants used in aerosols.
- Leave a line between different components of the dosage form, e.g. for capsule shell components, coating components.
- Complete "quantity" column as follows where appropriate: Insert ND for substances not detectable in the final formulation, e.g. solvents. Insert upper and lower limit if quantity not fixed e.g. for substance used to adjust pH.

NOTE FOR GUIDANCE ON THE PREPARATION OF SUMMARIES OF PRODUCT CHARACTERISTICS FOR NON-IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

1. INTRODUCTION

In accordance with Article 5a of directive 81/851/EEC as amended and Article 28 of Council Regulation (EEC) 2309/93. Any application for marketing authorisation submitted after 1 January 1992 must be accompagnied by the summary of product characteristics which is proposed by the applicant. Once they have completed the evaluation of the dossier, the Agency with its Committees or the competent authorities of the Member States approve the summary of product characteristics, if necessary, after suggesting certain amendments to the applicant to take account of the evaluation of the product.

In the case of veterinary medicinal products which were first authorised before 1 January 1992, the person responsible for marketing will be required to propose summaries of product characteristics for the products concerned during the five yearly renewal of marketing authorizations required by Directive 81/851/EEC.

The fundamental purpose of the summary of product characteristics is to provide a clear and unambiguous description of the approved conditions of use of a veterinary medicinal product in the European Community or Member State(s) concerned, presented in accordance with a single standardised layout. As such, the summary of product characteristics forms part of the marketing authorisation which is granted by the competent authorities of the Member States. It may be amended only with the express approval of the competent authority concerned.

The summary of product characteristics is intended to fulfil several objectives. The labelling, package insert and any data sheet must comply with the approved conditions of use set out in the summary of product characteristics. The SPC also provides an instrument for the control by the Agency with its Committtees or competent authorities of promotional material provided by the authorisation holder.

At the Community level, the SPC provides a basis for comparing the approved conditions of use of a particular veterinary medicinal product in the different Member States. When using the Community "decentralised" or "centralised" procedures, applicants must propose an identical SPC for all Member States. In the case of the decentralised procedure this SPC must also be identical with that approved by the Member State on whose authorisation the application is based. At the conclusion of the Community procedures, the Committee for Veterinary Medicinal Products always reviews the SPC in order to reach agreement on a single SPC for the product concerned which will apply throughout the Community. The CVMP will agree the summary of product characteristics as part of its opinion (with the exception of the information under points 6.5 and 7 which may differ from Member State to Member State.

The SPC is also used as a means of providing information to third countries about the conditions of use of a veterinary medicinal product within the Member States of the Community. In accordance with Article 24a of Directive 84/851/EEC, the competent authorities of a Member State will, upon request, provide the authorities of a third country with a copy of the SPC for the product concerned. Thus the regulatory authorities of third countries can easily obtain information about the officially authorised conditions of use of a product in the Community or a Member State.

The order of presentation of the SPC is specified in Article 5a of the Directive, and should always be followed. This order of presentation is set out on the following page.

2. SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME of the veterinary medicinal product
2. QUALITATIVE AND QUANTITATIVE COMPOSITION in terms of the active ingredients and constituents, knowledge of which is necessary for the proper administration of the medicinal product; the international non-proprietary names recommended by the World Health Organisation shall be used, or failing this, the usual non-proprietary name or chemical description
3. PHARMACEUTICAL FORM
4. PHARMACOLOGICAL PROPERTIES, and in so far as this information is useful for therapeutic purposes, pharmacokinetic particulars
5. CLINICAL PARTICULARS:

5.0. Target species
5.1 Inidcations for use, specifying the target species
5.2 Contra-indications
5.3 Undesirable effects (frequency and seriousness)
5.4 Special precautions for use
5.5 Use during pregnancy and lactation
5.6 Interaction with other medicaments and other forms of interaction
5.7 Posology and method of administration
5.8 Overdose (symptoms, emergency procedures, antidotes) (if necessary)
5.9 Special warnings for each target species
5.10 Withdrawal periods
5.11 Special precautions to be taken by the person administering the product to animals

6. PHARMACEUTICAL PARTICULARS

6.1 Incompatibilities (major)
6.2 Shelf-life, if necessary after reconstitution of the product, or when the container is opened for the first time
6.3 Special precautions for storage
6.4 Nature and contents of container

6.5 Name or style and permanent address or registered place of business of the holder of the authorization to place the product on the market

6.6 Special precautions for the disposal of unused product or waste material, if any

3. GENERAL CONSIDERATIONS FOR THE PREPARATION OF THE SPC

When preparing an SPC, it should be noted that the SPC is intended to provide a detailed objective summary of the conditions of authorisation of a veterinary medicinal product. The SPC is not a promotional document, nor is it intended to constitute a summary of the evaluation of the medicinal product by the competent authorities.

It follows that all the statements contained in the SPC must be justified by the contents of the application dossier which is submitted to the competent authority. Statements of a promotional nature such as "x is the treatment of choice for y" are not acceptable. Moreover, extraneous information such as the results of toxicity studies should not be included unless necessary to enable the practitioner to assess the benefits and risks of the use of the product in a particular case.

Particular care should be taken in ensuring that clear and unambiguous language is used throughout the SPC. Attention should be given to the clear definition of the scope of the inidications, contra-indications, precautions for use and warning statements to ensure that these clearly identify the groups or sub-groups of animals concerned.

The SPC must always be presented in the national language or languages of the Member State concerned by the application. Where the SPC has been translated from another language, particular care should be taken to ensure the accuracy of the translation and to ensure that appropriate terminology has been used in the different languages concerned. A copy of the original language version of the SPC should always be included in the authorisation file.

4. SPECIFIC CONSIDERATIONS FOR THE PREPARATION OF THE SPC

1. NAME of the veterinary medicinal product

The name of the veterinary medicinal product may be a brand name or a generic name

When selecting brand names, care should be taken to avoid the use of words or abbreviations which may give rise to confusion.

Where generic names are used, the generic name of the active ingredient should always be followed by the name of the authorisation holder, the manufacturer or the distributor, as appropriate.

Where a single brand or generic name is used to cover a range of veterinary medicinal products, the name of each product within the range should be completed by reference to:

- the concentration in terms of active ingredients;
- the pharmaceutical form, if necessary;
- the target species, if necessary.

2. Qualitative and quantitative composition

Full details of the qualitative and quantitative composition in terms of active ingredients should be provided.

In describing the *qualitative composition* of the product, the following principles should be followed:

- Where a substance is the subject of a monograph in the European Pharmacopoeia, or failing this, one of the pharmacopoeia of the Member States, the main title at the head of the monograph in question should be used to describe the substance concerned, with a reference to the monograph.
- In other cases, the international non-proprietary name (I.N.N.) recommended by the World Health Organisation should be used.
- In the absence of an I.N.N., the exact scientific designation should be given.
- Substances not having an I.N.N. or an exact scientific designation should be described by a statement of how and from what they were prepared.

Where the active ingredient is present in the form of the parent molecule, the standard terminology should be used (e.g. dexamethasone, levamisole).

Where the active ingredient is present as a salt or hydrate, this should be clearly stated e.g.:
- dexamethosone (as acetate);
- levamisol (as chlorhydrate).

Where the active ingredient is of a particular quality standard, for example in the case of active ingredients used in premixes for the manufacture of medicated feeding-stuffs, this should also be indicated, e.g.:
- neomycin (as sulphate) for the premixes for medicated feeding-stuffs.

For the description of the *quantitative composition*:

- Where the active ingredient is present in the form of a salt, derivative (e.g. ester) or hydrate, the quantitative composition must always be expressed in terms of the mass (or biological activity in International (or other) Units where appropriate) of the active moeity of the molecule which is present in the molecule (e.g. x mg levamisol in the form of levamisol sulfate). However, in the case of older compounds which have traditionally been expressed in the form of a salt, derivative or hydrate, it may in some case be appropriate to indicate the quantitative composition in terms of both the salt or derivative and the parent molecule (e.g. x mg levamisol sulfate, equivalent to y mg levamisol).
- In the case of unit dose preparations, the quantitative composition should also be stated per unit dose (e.g. x mg per mg or per ml; y mg per vial).
- In the case of solid or liquid preparation, the quantitative composition should be stated in terms of mg per g or per ml.

In addition to the qualitative and quantitative composition in terms of active principles, the qualitative and quantitative composition of the *EXCIPIENT* should be

stated, where knowledge of this is essential for the safe administration of the medicinal product.

The following examples, which are not exhaustive, are intended to illustrate the operation of this requirement:

- Colouring matters should always be mentioned, and the "E" numbers allocated to them should be included.
- Preservatives should always be mentioned, and any "E" numbers allocated should be indicated.
- In the case of premixes for medicated feeding-stuffs, information should be provided about the vehicle of the premix.

3. PHARMACEUTICAL FORM

If the product is not presented in the final pharmaceutical form intended for administration to animals, the final pharmaceutical form should be stated.

4. PHARMACOLOGICAL PROPERTIES, and in so far as this information is useful for therapeutic purposes, pharmacokinetic particulars;

Whenever possible, this section should be presented in accordance with the following sequence:

- Summary presentation of the active ingredient(s);
- Pharmacodynamic properties;
- Pharmacokinetic properties.

- SUMMARY PRESENTATION OF THE ACTIVE INGREDIENT

The following information should be given:

- The active ingredient;
- The therapeutic group;
- The pharmacological action, with the mechanism of action, if known;
- The group of substances to which it belongs;
- The mechanism of action, if known.

For example: "X is a bactericidal antibiotic belonging to the xx group which acts by inhibition of protein synthesis."

- PHARMACODYNAMIC PROPERTIES

The pharmacodynamic activity of the active ingredient(s) should be specified, together with the mechanism of the action, on the basis of the information contained in the application dossier.

- PHARMACOKINETIC PROPERTIES

Relevant information may be provided on the absorption, distribution, biotransformation and elimination of the product in each of the target species, for example:

Absorption:

- Percentage of the dose absorbed by the oral route;
- Time necessary to obtain the maximum concentration (T max);
- The maximum concentration (C max);
- Influence of feeding régime for absorption by the oral route;
- Quantity absorbed after topical administration.

Distribution:

- Existence of possible linearity between the concentrations obtained and the dose administered;
- Level of protein binding;
- Tissue distribution.

Biotransformation

- Information relating to metabolism.

Elimination

- Half life;
- Principal routes of excretion, including secondary routes which may be relevant from an environmental point of view.

5. CLINICAL PARTICULARS

5.0 Target species

The target species, and/or any sub-category should be indicated.

5.1 Indications for use, specifying the target species

The indications should be defined as precisely as possible and should be fully substantiated by the contents of the application dossier. In each case, indicate whether the treatment is for prophylactic, therapeutic or diagnostic purposes.

5.2 Contra-indications

Contra-indications result from a set of circumstances which make it undesirable to use a product. In particular, contra-indications may be linked with a target species, a group of animals or an individual animal, the administration of the product by a particular route or administration in conjunction with other products.

A contra-indication may be absolute or relative.

Absolute contra-indications must be clearly and unambiguously worded. They should also cover the possibility of the extra label use of the product in non-target species, where this is clearly contra-indicated by the results of the stuides or the scientific literature.

In certain circumstances, it may be necessary to state relative contra-indications to aid the prescriber to balance the potential benefits and risks of the use of the product in a specific situation.

5.3 Undesirable effects, frequency and seriousness

As appropriate, the following information should be provided for each undesirable effect; the nature of the effect, duration, itensity, frequency, reversibilty, effect on the general state of health of the animal and possible treatments. In addition, it should be indicated whether certain species or breeds or types of individual are

more susceptible to the undesirable effect concerned, or whether it is more frequent under certain types of husbandry conditions.

In the case of products intended for use in food-producing animals, any adverse effects on the quantity or quality of food-stuffs of animal origin should also be mentioned.

5.4 Special precautions for use

The purpose of this section is to warn prescribers and suppliers of the possibility of class or drug-related modifications of the safety or efficacy profile of the product which may arise in particular situations such as renal, hepatic or cardiac failure, or in very old or very young animals and to describe the conditions under which the medicinal product may be recommended for use in such groups provided the special precautions are followed.

5.5 Use during pregnancy and lactation

In order to ensure the safe use of the product, the practitioner must be informed of the information necessary and recommendations for the use of the product in pregnant animals and lactating animals. Obviously, this section has no relevance in the case of products intended exclusively for very young animals or for males. In other cases, information about use during pregnancy or lactation may have been provided in the sections dealing with contra-indications or special precautions for use. In such cases, a cross reference to the relevant section will be sufficient. Examples of the type of additional information which might usefully be included in this section are:

"Laboratory studies in the rat and the rabiit have not produced any evidence of a teratogenic effect."

"When administered to lactating females, residues of x are present in the maternal milk. Since no studies have been reported of the effects on the development of new born young of the ingestion of this milk, it would be prudent not to feed very young animals with milk obtained from the mother."

Information about the consequences of residues for the use of milk for human consumption should be given in section 5.10, withdrawal periods.

5.6 Interaction with other medicaments and other forms of interaction

The concomitant use of two or more veterinary medicinal products may give rise to interactions of a pharmacokinetic or a pharmacodynamic nature which may result in additonal or increased adverse effects, or which may result in the failure of efficacy of the product concerned.

In certain cases, the nature or risk of interactions will be such that the use of a particular product will be contra-indicated in absolute or relative terms while another substance or product is administered to animals. In such cases, the relevant information should be given in the section dealing with contra-indications, and a cross-reference should be included in this section.

In other cases, information should be provided in this section about the nature, mechanism and effects of interactions, with details of any corrective action which may need to be taken.

In addition to interactions between medicinal products, consideration should be given to other interactions with elements in the animals' diet and additives, for example.

5.7 Posology (dosage) and mehtod of administration

Where necessary, the *POSOLOGY* must be indicated for each target species and each therapeutic indication. Where the posology is expressed in active principle it should be given in terms of mg per kg of live bodyweight.

Where the posology is expressed in terms of a veterinary medicinal product, (for example by unit doses or by a volume of injectable solution), it should be given both in terms of the amount to be administered to the animal and the equivalent in terms of mg per kg of bodyweight, for example:

- 120 mg tablet, equivalent to 5 mg/kg;
- 10 mg/kg orally, as 20 ml/l drinking water.

The frequency of treatment should be stated in hours or days for each target species and the total duration of treatment should be stated.

The description of the method of administration should include all the information necessary to enable the user to administer the product successfully to the target species, including the method of administration, the site of administration and any special equipment which is necessary. Where necessary, information should be provided on the timing of administration in relation to feeding, milking, exercise etc.

In addition, any necessary guidance should be given on the adjustment of the dosage to take account of the disease status of the animal, and of the possibility of a reduced intake of feed or water by sick animals.

5.8 Overdose

If necessary, the following information should be provided:

- Symptoms, nature, evolution, seriousness, duration;
- Available symptomatic treatments;
- Emergency procedures;
- Antidotes, if no antidote is available, this should be clearly stated.

5.9 Special warnings for each target species

The purpose of this section is to provide for the detailed, clear and precise statement of any physico-chemical, pharmacological, toxicological or clinical information, knowledge of which is necessary in order to ensure the safe and effective use of the medicinal product.

Where appropriate, information may also be provided about possible risks resulting from the extra-label use of the product.

5.10 Withdrawal periods

In Community legislation, the withdrawal period is defined as the period between the last administration of the veterinary medicinal product to animals and the production of food-stuffs from such animals.

If necessary, different withdrawal periods should be stated for meat and offal, milk, eggs and honey. Withdrawal periods should be indicated in days, using arabic numerals. A zero withdrawal period should be expressed as "0".

However, for fishmeat, the withdrawal period should be stated in degree days. The number of degree days is divided by the average water temperature, in °C, to give the withdrawal period in days.

In the case of bolus and other sustained release preparations, the withdrawal period should be calculated from the date of the physical administration of the product to the animal.

In certain instances, the use of a veterinary medicinal product will be formally contra-indicated for use in animals during the phase in which they produce food for human consumption. For example, the product may be authorised for use in dairy cattle only during the dry period, or authorised only for use in broilers and not in laying birds. Alternatively, a product may be indicated only for animals which are not used for food production. Although such restrictions on use will already have been indicated in the sections describing the target species, the indications and contra-indications, they should be repeated in this section, for example:

"Withdrawal period: meat and offal: *n* days

milk: x is not permitted for use in lactating dairy cattle.
In the event of premature lactation, discard the milk obtained during the first *n* days."

5.11 Special precautions to be taken by the person administering the product to animals

Mention should be made of any risks resulting from the nature of the product, its preparation and use and of any risks resulting from the particular characteristics of the user. Any recommendations for the use of protective clothing during the preparation or administration of the product to animals should be clearly and unambiguously stated. Similarly, clear guidance should be provided on any remedial action to be taken following accidental contact with the product, either through spillage or accidental self-injection. In some cases recommendations for appropriate action will be linked with particular characteristics of the user, such as a susceptibility to allergies or to asthma.

6. PHARMACEUTICAL PARTICULARS

6.1 Incompatibilities (major)

In this section information should be given about physical or chemical incompatibilities of the product with others with which it is likely to be mixed or co-administered. This may be particularly important for products to be diluted before parenteral administration. Significant problems of sorption of product to syringes, large volume parenteral containers etc. should be stated. Similarly, in the case of premixes for medicated feeding-stuffs, any restriction on the range of feeds which may be used for the preparation of the final feed should be indicated.

6.2 Shelf-life

The shelf-life should be expressed in arabic numerals as a number of years or months. If the storage temperature required is less than 25°C, the storage temperature should also be indicated.

In the case of multi-dose preparations presented in sealed containers, or where reconstitution of the product is required before administration to animals, the shelf-

life of the broached or opened container/reconstituted product should also be stated. Similarly, in the case of premixes for medicated feeding-stuffs, the shelf-life should be indicated for the premix, and for the medicated feed.

6.3 Special precautions for storage

Temperature, light and humidity may all effect the storage of a veterinary medicinal product.This section will contain the information necessary for the correct storage of the product, e.g.:

"- Do not store at temperatures above/below n°C";
"- Store out of direct sunlight";
"- Store in a dry place".

6.4 Nature and contents of container

A summary but complete description of the contents of the final sales presentation should be provided. Where a single SPC covers a range of products, this information should be provided for each product in the range.

6.5 Name or style and permanent address or registered place of business of the holder of the authorisation to place the product on the market

Where different, the name and address of the manufacturer should also be given.

6.6 Special precautions for the disposal of unused product or waste materials, if any

This section should include information necessary for the safe disposal of unused product, and the equipment used for the administration of the product to animals.

In addition, reference should be made to any restrictions on the disposal of waste products from treated animals.

7. Final information

At the end of the SPC, the following information should be provided:

- The marketing authorisation number of the product(s) concerned, if known;
- The date of the approval/last revision of the SPC, as relevant;
- The conditions of supply of the veterinary medicinal product to animal owners.

NUMBER OF COPIES OF THE DOSSIER AND WRITTEN RESPONSES : NON-IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

Number of copies	BE	DK	DE	GR	ES	FR	IR	IT	LU[1]	NL	PO	UK	FI	SV	A
- full dossiers	1	1	3	1	4	3	2	2	0	4	1	4	1	1	2
- additional copies of Part I summary + expert reports	4	2	1	2	2	22	1	3	0	6	6	12	1	3	1
- additional copies of Part II quality	3		0	1	1		1	1	0	1	2				1
- additional copies of Part III safety and residue studies			0					1			2			1	
- consolidated responses to questions	2	2	4	1	4	3	1	2	0	5	3	4	2	4	3

1. In Luxembourg, a single copy of parts I and II are required if the application is for the recognition of an authorization already granted by another Member State.

ACCEPTABLE LANGUAGES : NON-IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

Languages	BE	DK	DE	ES	FR	GR	IR	IT	LU[1]	NL	PO	UK	FI	SV	A
In principle	Fr or Nl	D k	De	Es	Fr	Gr	En	It	Fr	Nl	Po	En	Fin Sw e	Swe	De
Other languages acceptable for Part II Pharmaceutical	De or En	En	En	En or Fr		En		En or Fr	De or En	De or En	En or Fr		En	En	En
Part III Safety + Residues Part IV Clinical	De or En	En	En	En or Fr	En[1]	En		En or Fr	De or En	De or En	En or Fr		En	En	En
Summaries of the dossier[3] Expert Reports	De or En	En	En [2]	En or Fr		En		En or Fr[2] 4	De or En	De or En	En or Fr [2]		En	En	En

1. In France, each study or test is accepted in the language mentioned, if accompanied by a very detailed and precise summary in the national language containing, in particular, reference to the pages containing the data in question.
2. The submission of these summraries in the national language is, however, preferred.
3. Part IB, the Summary of Product Characteristics, must always be translated into the official language(s) of the Member State concerned.
4. The submission of the expert reports in the Italian language is however preferred.

PROVISION OF SAMPLES OF NON-IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

Number of samples	BE	ES	FR	GR	IR	LU	PO	A	SV
Finished product	1*	x	x	x	x	1*	1*	x	x*
All active substances		x						x	x
Only active substances for which the applicant has introduced a monograph	2x								
Non-active substances for which the applicant has introduced a monograph	2x						x		

Notes

* the appropriate number of samples should be provided in the form of the final sales presentation of the product (Be, Port and Lux). For Portugal, samples should always be accompanied by a certificate of analysis.

x in other cases, the sample should be provided in sufficient quantity to permit the full assay and verification of the control methods used by the manufacturer

In the other Member States, Dk, De, It, Nl, UK and Fin, samples should be provided only upon request of the competent authorities.

NUMBER OF COPIES OF THE DOSSIER AND WRITTEN RESPONSES: IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

Number of copies	BE	DK	DE	GR	ES	FR	IR	IT	LU[2]	NL	PO	UK	FI	SV	A
- full dossiers	1	1	3[1]	1	5	3	1	2	0	3	5	5	1	1	2
- additional copies of Part I summary + expert reports	4	2		2	4	22		3	0	6		10	1	3	1
- additional copies of Part II quality	3			1	1			1	0						1
- consolidated responses to questions	2	2	3	1	5	3	2	2	0	3	2	5	1	4	3

1. In addition, 5 copies of the draft leaflets for the product are required and 4 copies of the national application form, which may be replaced by the EEC application form.

2. In Luxembourg, a single copy of parts I and II are required if the application is for the recognition of an authorization already granted by another Member State.

ACCEPTABLE LANGUAGES : IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

Languages	BE	DK	DE	ES	FR	GR	IR	IT	LU[1]	NL	PO	UK	FI	SV	A
In principle	Fr or Nl	Dk	De	Es	Fr	Gr	En	It	Fr	Nl	Po	En	En	Sv	De
Other languages acceptable for Part II Pharmaceutical	De or En	En	En	En or Fr		En		En or Fr	De or En	De or En	En or Fr			En	En
Part III Safety + Residues Part IV Clinical	De or En	En	En	En or Fr	En[1]	En		En or Fr	De or En	De or En	En or Fr			En	En
Summaries of the dossier[3] Expert Reports	De or En	En	En[2]	En or Fr		En		En or Fr[2] 4	De or En	De or En	En or Fr[2]			En	En

1. In France, each study or test is accepted in the language mentioned, if accompanied by a very detailed and precise summary in the national language containing, in particular, reference to the pages containing the data in question.
2. The submission of these summraries in the national language is, however, preferred.
3. Part IB, the Summary of Product Characteristics, must always be translated into the official language(s) of the Member State concerned.
4. The submission of the expert reports in the Italian language is however preferred.

PROVISION OF SAMPLES OF IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

Number of samples	BE	ES	FR	GR	IR	FI	A	SV
Finished product	1*	x	x	x	x	1	x	x*
All active substances		x						
Only active substances for which the applicant has introduced a monograph	2x							
Non-active substances for which the applicant has introduced a monograph	2x							

Notes

* the appropriate number of samples should be provided in the form of the final sales presentation of the product (Be)

x in other cases, the sample should be provided in sufficient quantity to permit the full assay and verification of the control methods used by the manufacturer

In the other Member States, Dk, De, It, Lux, Nl, Por, UK and Fin, samples should be provided only upon request of the competent authorities.

DOSSIER CHECK-IN PROCEDURE

National application number:

Date of entry Date of decision

Conclusion file accepted O not accepted O

	Yes	No	Language
Part I			
Application forms	O	O	[----]
Summary of product characteristics	O	O	[-----]
Expert Report			
Quality	O	O	[-----]
Pharmacology/Toxicology	O	O	[-----]
Residues	O	O	[-----]
Clinical	O	O	[-----]
Proof that fees have been paid	O	O	
All pages present and legible	O	O	
Draft packaging	O	O	[-----]
Draft package insert in national language	O	O	
Draft SPC in national language	O	O	
Manufacturers' authorisation			
of finished product	O	O	[-----]
Marketing authorisation(s)	O	O	[-----]
Sample(s)	O	O	
Part I acceptable	O	O	

Not acceptable for reasons.....

Part II/II bis			
Chemical, Pharmaceutical			
and Biological documentation O	O		[-----]
Drug Master File O	O		[-----]
All volumes present	O	O	
All pages present and legible	O	O	
Part II/II bis acceptable	O	O	

Not acceptable for reasons.....

Part III

Pharmaco-Toxicological Documentation	O	O	[-----]
All volumes present	O	O	
All pages present and legible	O	O	
Residues Documentation	O	O	[-----]
All volumes present	O	O	
All pages present and legible	O	O	

Part III acceptable O O

Not acceptable for reasons.....

Part IV

Clinical Documentation	O	O	[-----]
All volumes present	O	O	
All pages present and legible	O	O	

Part IV acceptable

Not acceptable for reasons.....

Abridged application

	Yes	No
<u>Application according to Directive 81/851/EEC Article 5 point 10(a)i</u>		
Letter of consent from the holder of the authorisation of the original proprietary medicinal product for reference to		
Part III	O	O
Part IV	O	O
<u>Application according to Directive 81/851/EEC Article 5 point 10(a)iii</u>		
Evidence that an essentially similar product has been authorised within the Community in accordance with Community provision in force for not less than six/ten years	O	O
Evidence that an essentially similar product is marketed in the Member State for which an application is made	O	O

<u>For immunological veterinary medicinal products</u>

Part V acceptable O O

Not acceptable for reasons.....

LIST OF OFFICIAL JOURNALS

In accordance with Article 40 of Directive 81/851/EEC, all decisions to grant marketing authorization must be published. The name and address of the Official Journal in each Member State is given below.

Austria *(to be entered when available)*

Belgium **Belgisch Staatsblad/Moniteur Belge**
Leuvensestraat 40-42/Rue de Louvain 40-42,
BRUSSELS

Denmark **Statstidende**
Otto Mønsteds Gade 3,
DK-1571, KØBENHAVN V

Finland **Virallinen Lehti, Officiella tidningen**
P.O. Box 23
SF - 00431 HELSINKI

France **Journal Officiel de la République Française**
rue Desaix, F-75727 PARIS

Germany **Bundesanzeiger Verlags-GmbH**
Postfach 10 05 34, D-50445 KÖLN

Greece **Ephimeris Kyvernisseos Ellenikis Dimokratias**
(Official Journal, Government Publications)
Kapodistriou 34, ATHENS

Ireland **Iris Oifiguil**, Stationery Office
Bishop Street, DUBLIN 8

Italy **Gazzetta Ufficiale della Reppublica Italiana**
Istituto Poligrafico e Zecca dello Stato
Piazza G. Verdi 10, I-00198 ROMA

Luxemburg **Mémorial** Service Central de Législation
boulevarde F D Roosevelt,
L - 2450 LUXEMBURG

Netherlands **Nederlandse Staatscourant**
Postbus 20014, NL-2500 EA DEN HAAG

Portugal **Diario da Republica** Casa da Moeda EP
Rua D. Francisco Manuel de Melo 5 1092 LISBOA Codex

Spain	**Boletin Oficial de Estado** Trafalgar 27 28010 MADRID		
Sweden	**Post-och Inrikes Tidningar** Bamängsgatan 21 P.O. Box 4731 S - 116 92 STOCKHOLM		
United Kingdom	**London Gazette** HMSO Publications Centre 51 Nine Elms Lane LONDON SW8 2DR	**Edinburgh Gazette** 55 Lothian road EDINBURGH EH3 9AZ	**Belfast Gazette** Chichester House Chichester Street BELFAST BT1 3JY
European Union	**Official Journal of the European Communities** Office for Official Publications of the European Communities 2 rue Mercier L - 2985 LUXEMBURG		

ADDRESSES FOR DELIVERY OF THE DOSSIER AND SUBSEQUENT CORRESPONDENCE

VETERINARY MEDICINAL PRODUCTS
OTHER THAN IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

N.B. Unless otherwise indicated, information about the national fees payable for the evaluation of an application may be obtained from the first address indicated below.

Austria

Bundesministerium für Gesundheit und Konsumentenschutz

Pharmazeutische Angelegenheiten

Radetzkystrasse 2

A-1031 WIEN

Tel 43 1 71 172 46 55

Fax 43 1 71 492 22

Belgium

Ministry of Public Health and the Environment

Pharmaceutical Inspectorate

Secrétariat of the Medicines Commission

Quartier Vésale

B - 1010 BRUXELLES

Tel 32 2 210 48 96

Fax 32 2 210 48 80

Denmark

Sundhedsstyrelsen

Lægemiddelafdelingen

378 Frederikssundsvej

DK - 2700 BRONSHOJ

Tel 45 44 94 36 77

Fax 45 44 94 02 37

Telex 35333 IPHARM DK

France

Ministère de l'Agriculture et de la Forêt

CNEVA (Centre National d'Etudes Vétérinaires et Alimentaires)

Laboratoire des Médicaments Vétérinaires

Javené

F - 35133 FOUGERES

Tel 33 99 94 78 72

Fax 33 99 94 78 99

Germany

Bundesinstitut für gesundheitlichen

Verbraucherschutz und Veterinärmedizin

Fachbereich 6

Diedersdorfer Weg 1

D - 12277 Berlin

Tel 49 30 7236 2364

Fax 49 30 7236 2955

Greece

National Drug Organisation (ΕΟΦ)

284 Mesogion Avenue

GR - 15562 ATHENS

Tel 30 1 654 51 94

Fax 30 1 654 55 35

Ireland

National Drugs Advisory Board

Charles Lucas House

63/64 Adelaide Road

IRL - Dublin 2

Tel 353 16 76 49 71-7

Fax 353 16 76 78 36

Italy

Ministero della Sanità

Direzione Generale dei Servizi Veterinari-Divisione IX

Ministero della Sanità

Piazzale Marconi 25

IT - 00144 ROME

Tel 39 6 599 436 76

Fax 39 6 599 43 584

Luxembourg

Direction de la Santé

Division de la Pharmacie et des Médicaments

10 rue C M Spoo

L - 2546 LUXEMBOURG

Tel 352 478 55 92

Fax 352 22 44 58

Netherlands

Bureau Registratie Diergeneesmiddelen

Postbus 289

NL -6700 AG Wageningen

Tel 31 8370 75491

Fax 31 8370 23193

Portugal

IPPAA-Centro Nacional de Protecçao e Controlo Zoo-Sanitario

Lg da Academia Nacional de Belas Artes 2

P - 1294 LISBOA CODEX

Tel 351 1 346 51 65

Fax 351 1 346 35 18

Spain

Ministerio de Agricultura
Subdireccion General de Sanidad Animal
Direccion General de Sanidad de la Produccion Agraria
C/ Velzquez, 2a planta
E - 28002 Madrid
Tel 34 1 347 83 04
Fax 34 1 347 82 99

A copy of the application should also be sent to :
Subdireccion General de Evaluacion de Medicamentos
Ministerio de Sanidad y Consumo
Paseo de Prado 18-20
E - 28014 Madrid
Tel 34 1 596 40 40
Fax 34 1 596 40 69

United Kingdom

Veterinary Medicines Directorate
Woodham Lane
New Haw, Addlestone
GB - SURREY KT15 3NB
Tel 44 1932 33 69 11
Fax 44 1932 33 66 18

Finland

National Agency for Medicines
Marketing Authorisation
Mannerheimintie 166
PO Box 55
Fin-00301
Helsinki
Tel: 358 0 47 441
Fax: 358 0 47 445 25

Sweden

Medical Products Agency

Husargatan 8

P.O. Box 26

S-75103 UPPSALA

Tel 46 18 17 46 00

Fax 46 18 54 85 66

European Agency for the Evaluation of Medicinal Products (EMEA)

Westferry Circus

Canary Wharf

GB-LONDON E14 4HB

Tel: 44 171 418 84 00

Fax: 44 171 418 84 16

IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

N.B. Unless otherwise indicated, information about the national fees payable for the evaluation of an application may be obtained from the first address indicated below.

Austria

Bundesministerium für Gesundheit und Konsumentenschutz

Pharmazeutische Angelegenheiten

Radetzkystrasse 2

A-1031 WIEN

Tel 43 1 71 172 46 55

Fax 43 1 71 492 22

Belgium

Ministry of Public Health and the Environment

Pharmaceutical Inspectorate

Secrétariat of the Medicines Commission

Quartier Vésale

B - 1010 BRUXELLES

Tel 32 2 210 48 96

Fax 32 2 210 48 80

Denmark

Sundhedsstyrelsen

Lægemiddelafdelingen

378 Frederikssundsvej

DK - 2700 BRONSHOJ

Tel 45 44 94 36 77

Fax 45 44 94 02 37

France

Ministère de l'Agriculture et de la Forêt

CNEVA (Centre National d'Etudes Vétérinaires et Alimentaires)

Laboratoire des Médicaments Vétérinaires

Javené

F - 35133 FOUGERES

Tel 33 99 94 78 72

Fax 33 99 94 78 99

Germany

Paul Ehrlich Institut

Bundesamt für Sera und Impstoffe

Paul-Ehrlich Strasse 51-59

D - 6070 Langen 1

Tel 49 06103 77 0

Fax 49 06103 77 1234

For vaccines for foot and mouth disease, hog cholera and exotic diseases a copy of the dossier should be sent to :

BFA Tübingen

P.O. Box 1149

D - 7400 Tübingen

Tel 49 07071 6031

Fax 49 07071 603201

Greece

National Drug Organisation (ΕΟΦ)

284 Mesogion Avenue

GR - 15562 ATHENS

Tel 30 1 654 51 94

Fax 30 1 654 55 35

Ireland

Department of Agriculture, Food and Forestry

Agriculture House

Kildare Street

IRL - Dublin 2

Tel 353 1 678 90 11

Fax 353 1 661 62 63

Italy

Direttore Generale

Direzione Servizi Veterinari

Ministero della Sanità

Piazzale Marconi 25

IT - 00144 ROME

Tel 39 6 592 67 80

Fax 39 6 592 58 57

One further copy of the application should be submitted to :

Direttore

Laboratorio di Medicina Veterinaria

Istituto Superiore di Sanita

Viale Regina Elena 299

I - 00161 Roma

Tel 39 6 444 00 77

Fax 39 6 444 00 77

Luxembourg

Direction de la Santé

Division de la Pharmacie et des Médicaments

10 rue C M Spoo

L - 2546 LUXEMBOURG

Tel 352 478 55 92

Fax 352 22 44 58

Netherlands

Bureau Registratie Diergeneesmiddelen

Postbus 289

NL - 6700 AG Wageningen

Tel 31 8370 75 491

Fax 31 8370 23 193

Portugal

IPPAA-Centro Nacional de Protecçao e Controlo Zoo-Sanitario
Lg da Academia Nacional de Belas Artes 2
P - 1294 LISBOA CODEX
Tel 351 1 346 51 65
Fax 351 1 346 35 18

Spain

Ministerio de Agricultura
Subdireccion General de Sanidad Animal
Direccion General de Sanidad de la Produccion Agraria
C/ Velazquez n° 147, 2a planta
E - 28002 Madrid
Tel 34 1 347 83 04
Fax 34 1 347 82 99

A copy of the application should also be sent to :
Subdireccion General de Evaluacion de Medicamentos
Ministerio de Sanidad y Consumo
Paseo de Prado 18-20
E - 28014 Madrid
Tel 34 1 596 40 40
Fax 34 1 596 40 69

United Kingdom

Veterinary Medicines Directorate
Woodham Lane
New Haw, Addlestone
GB - Surrey KT15 3NB
Tel 44 1932 33 69 11
Fax 44 1932 33 66 18

Finland

The application should be sent to:

Ministry of Agriculture and Forestry

Veterinary and Food Department

PO Box 232

FIN-00171 Helsinki

Tel 358 0 1601

Fax 358 0 160 33 38

The full dossier, the additional copies and samples:

Veterinary Officer DVM U. Rikula

Ministry of Agriculture and Forestry

c/o National Veterinary and Food Research Institute

PO Box 368

FIN-00231 Helsinki

Tel 3580 393 101

Fax 3580 393 18 64

Sweden

Medical Products Agency

Husargatan 8

P.O. Box 26

S-75103 UPPSALA

Tel 46 18 17 46 00

Fax 46 18 54 85 66

European Agency for the Evaluation of Medicinal Products (EMEA)

Westferry Circus

Canary Wharf

GB-LONDON E14 4HB

Tel: 44 171 418 84 00

Fax: 44 171 418 84 16

GLOSSARY

Applicant: A (legal) person or company making an application for marketing for a national or centralised authorisation. If successful, an applicant becomes a marketing authorisation holder.

Arbitration rapporteur (mutual recognition): Member of the CPMP appointed to prepare a report after notification by the originating and concerned Member States that there are serious public health issues which remain in relation to the product at the end of the 90 day clarification and dialogue phase of the procedure.

ATC: Anatomical Therapeutic Chemical.

ATC classification: The 'Guidelines for ATC Classification' are published jointly by:

The WHO Collaborating Centre for Drug Statistics Methodology
PO Box 100 VEITVET
N-0518 Oslo 5

and

The Nordic Council for Medicines
PO Box 607
S-751 25 Uppsala

Catalogue references : ISBN 0802-8753
ISBN 82-90312-12-1

Check-in application: Administrative confirmation by a competent authority (Member State or EMEA as appropriate) that:

- the application is made according to the requirements of Articles 1 & 2 of Directive 75/319/EEC (i.e. that it contains Expert Reports),
- that fees have been paid where this is required before evaluation commences,
- that the physical completeness of the dossier is verified (Parts 1 to IV), and
- that the documentation is translated into national languages as required

Co-rapporteur (centralised): A second member of the Committee contributing to the assessment of a centralised application. The need for and specific role of the co-rapporteur is defined on a case-by-case basis by the Committee.

Committee for Veterinary Medicinal Products: A scientific committee set up to facilitate the adoption of common decisions by the Member States on the authorisation of veterinary medicinal products on the basis of scientific criteria of safety, quality and efficacy. The Committee is part of the EMEA.

Competent authority: An authority in a Member State responsible for the authorisation and supervision of medicinal products.

Concerned Member State (mutual recognition): Member State which is included in an application for mutual recognition.

European Agency for the Evaluation of Medicinal Products (EMEA): Agency established under Council Regulation 2309/93 responsible for coordinating the scientific resources put at its disposal by the competent authority of the Member States for the evaluation and supervision of medicinal products. It comprises the CPMP, CVMP, the Secretariat, the Executive Director and the Management Board.

Evaluation team (centralised): Experts nominated by the rapporteur/co-rapporteur from the lists of experts transmitted by the competent authorities in accordance with Article 51 of Regulation 2309/93 with proven experience in the assessment of medicinal products.

Expert Report: Report drawn up according to Directive 75/319/EEC on Quality, Safety or Efficacy by an expert, on behalf of the applicant including a tabulation, a written summary (optional) and a critical discussion of the properties of the product.

GMO medicinal product: Product containing or consisting of a Genetically Modified Organism (an organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination).

Parallel national application: Applications made in the transition period 1 January 1995 to 1 January 1998 at the same time to two or more competent national authorities in the EC.

Rapporteur (centralised): Member of the CPMP appointed to coordinate the evaluation of an evaluation of an application, taking into account any proposal from the applicant for choice of rapporteur.

Reference Member State: The Member State whose Assessment Report is used as the basis for mutual recognition Type II variations in other concerned Member State(s). Also used as a synonym for 'Originating Member State' in mutual recognition marketing authorisation applications (q.v.).

Scientific committees of the European Medicines Evaluation Agency: The Committee for Proprietary Medicinal Products (CPMP) and the Committee for Veterinary Medicinal Products (CVMP).

Summary of Product Characteristics: Text prepared according to Article 4(a) of Directive 65/65/EEC describing the properties of the product as authorised.

Tests, Studies and Trials: Investigations done to demonstrate quality, preclinical and clinical safety, ecotoxicity and efficacy of a medicinal product.

Trials: See tests.

Type I variation: a minor variation defined in Article 2 of the Variations Regulation (XX/95) and listed in Annex 1 of those Regulations provided that the conditions for such a variation laid down in the Annex are met.

Type II variation: A major variation which cannot be deemed to be a Type 1 variation and which is not a change leading to a new application as stated in Annex 2 of the Regulation (XX/95).

Urgent safety restriction: An interim change to product information by the marketing authorisation holder restricting the indication(s) and/or dosage, [and/or target species] of the medicinal products and/or warning due to new information having a bearing on the safe use of the product.