COMMISSION OF THE EUROPEAN COMMUNITIES

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Future system for the free movement of medicinal products
in the European Community

Proposal for a

COUNCIL REGULATION (EEC) SYN 309

laying down Community procedures for the authorization
and supervision of medicinal products
for human and veterinary use and establishing
a European Agency for the Evaluation of Medicinal Products

Proposal for a

COUNCIL DIRECTIVE SYN 310

amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC
in respect of medicinal products

Proposal for a

COUNCIL DIRECTIVE SYN 311

amending Directives 81/851/EEC and 81/852/EEC
in respect of veterinary medicinal products

Proposal for a

COUNCIL DIRECTIVE SYN 312

repealing Directive 87/22/EEC on the approximation
of national measures relating to the placing on the market
of high technology medicinal products
particularly those derived from biotechnology

(presented by the Commission)

EXPLANATORY MEMORANDUM ON THE FUTURE SYSTEM FOR THE FREE MOVEMENT OF MEDICINAL PRODUCTS IN THE EUROPEAN COMMUNITY

EXPLANATORY MEMORANDUM

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SUMMARY

Future system for the free movement of medicinal products in the European Community

Following the intensive consultations which have taken place over the past two years, the Commission is now presenting its proposals for the future system for the free movement of medicinal products (both for human and veterinary use) within the Community. These consultations have shown the existence of wide support for the main features of these proposals, including:

- the establishment of a new European Agency for the Evaluation of Medicinal Products;
- the creation of a new centralized Community procedure, compulsory for biotechnology products and veterinary medicines used as performance enhancers, and available on an optional basis for other innovatory medicinal products, leading to a Community authorization, valid throughout all 12 Member States;
- a decentralized procedure, based on the principle of mutual recognition, which will allow the progressive extension of a marketing authorization from one Member State to the others, with important safeguards to ensure that there is no dilution of the strict standards of quality, safety and efficacy.

The new Agency will be made up of the existing Committee for Proprietary Medicinal Products and the Committee for Veterinary Medicinal Products, with substantial additional logistical and administrative support. Its task will be to coordinate the work of evaluation and supervision of medicinal products being conducted in Member States to avoid duplication of effort, but at the same time ensure that all relevant factors are taken into consideration during the authorization process, and the subsequent supervision of medicines through adverse reaction monitoring (pharmacovigilance) and inspection and control of manufacturers.

In the case of applications submitted through the centralized procedure, following the evaluation of the application, the decision on whether or not to grant authorization will be taken by the Commission, in cooperation with the Member States. Thereafter, the Community will be responsible for the monitoring of the product, and the technical updating of the authorization. In the case of veterinary medicinal products intended for use as performance enhancers in farm animals, consideration is being given to Community arrangements to assess the impact of their use.

However, it is the decentralized procedure which will continue to be the most widely used after 1992. In this procedure, the Agency will only be involved if there is a disagreement between Member States about the quality, safety or efficacy of a medicinal product. In this case, the Agency will provide an independent scientific evaluation of the issues involved, and a binding arbitration procedure at Community level will follow. The monitoring of the product will remain the responsibility of the individual Member States. By 1996, this procedure will become the most commonly used for obtaining authorization for products intended for use in more than one Member State.

Both procedures will come into force in 1993, and will be reviewed, in the light of experience, in 1999-2000.

Future system for the free movement of medicinal products in the European Community

1. GENERAL CONSIDERATIONS

1.1. State of consultations

During the preparation of these proposals, the services of the Commission have engaged in an intensive round of consultations with the Member States, representatives of the pharmaceutical industry, representatives of consumer groups and the Consultative Committee for Consumers, and with European representatives of the various health professions concerned, in particular, pharmacists, doctors and veterinarians. Three consultation documents have been issued by the Commission or its services:

- the Report on the Activities of the Committee for Proprietary Medicinal Products (COM (88) 143 final of 22 March 1988);
- the "Memorandum on the future system for the authorization of medicinal products in the European Community, April 1989";
- a further discussion document on the future system of December 1989 (III/8267/89 Rev 2.).

All the detailed comments received in response to these documents have been carefully analysed and taken into consideration during the formulation of these proposals.

1.2. The objectives of the future system

Following this lengthy consultation exercise, there now appears to be general agreement on the objectives of the future system. These objectives can be presented from three points of view, without, however, attempting to present them in any order of priority:

- from the point of view of the protection of public health within the Community;
- from the industrial policy point of view;
- from the point of view of the interests and objectives of the Community.

From the point of view of public health:

a) A scientific evaluation of dossiers for authorization by the best European experts which can be recognized throughout the Community;

b) Criteria of quality, safety and efficacy based upon rigorous requirements imposed by harmonized Community legislation;

c) Clearly defined political and legal responsibilities for each authority dealing with the authorization of medicinal products in the Community and the refusal or withdrawal of products from the market;

d) A capacity to authorize the marketing of a new medicinal product as rapidly as possible so that it can be available to all patients throughout the Community;

e) A capacity to restrict or withdraw a medicinal product from the market throughout the Community as rapidly as possible on the basis of reliable information collected through a European pharmacovigilance network (adverse effects) and surveillance network (defective lots, counterfeiting);

f) Identical published information on the conditions of marketing a medicinal product valid throughout the Community:

- a single summary of product characteristics;
- identical labelling and patient information leaflet in the different languages of the Community;
- same legal status for obtaining the product (hospital use only, prescription only, self-medication,...);

g) A reinforcement of preclinical and clinical research facilities in Europe, so as to develop the expertise and knowledge necessary for the protection of public health;

From the point of view of Industrial policy:

a) Uniform, clear and well-known requirements for the presentation and content of application dossiers (EEC Guidelines and Notice to Applicants);

b) Deposit of a single file, if possible to a single competent authority in order to protect confidentiality and reduct the administrative burden (small number of copies; simplification of administrative requirements);

c) Simple, transparent, fair and non-bureaucratic procedures, respecting the time limits established by Community law;

d) Objective criteria for evaluation, based exclusively on the quality, safety and efficacy of the product, expressed in evaluation reports;

e) Rights to a hearing, to detailed reasons for decisions and appeal mechanisms for the applicant;

f) Reasonable registration fees corresponding to the true level of control and verification undertaken by the competent authority.

Aspects of specific Community interest:

a) the possibility of European concertation with innovatory companies during the research and development stage;

b) the pooling of expertise for the evaluation of innovatory products and the promotion of cooperation between Member States;

c) a single scientific evaluation valid for the whole Community;

d) allowing companies with a Community vocation direct access to a Community-scale market, while maintaining local/regional systems for other firms;

e) to provide a credible European authorization, which may be an aid to exports;

f) a single management of Community authorizations (renewals and variations);

g) coordination of the implementation of Community obligations (GMPs, GLPs, GCPs etc);

h) updating and international harmonization of testing requirements.

1.3. The two Community procedures

It appears that these objectives can best be met by a nuanced approach involving two procedures; one decentralized and the other centralized. The primary objective of the decentralized procedure will be to enable pharmaceutical companies to increase progressively their penetration from one national market to an increasing number of Member States. The objective of the centralized Community procedure, on the other hand, is to provide major innovatory products with direct access to a Community-scale market. The scope of these Community procedures will be revised in the light of the experience acquired after a reasonable period of time (e.g. for the year 2000).

The decentralized procedure will continue to be the most frequently used, even after 1992. A company which has obtained authorisation in one Member State will be able to apply for the acceptance of the authorization in one or more of the other Member States. If the Member States concerned consider that they cannot accept the authorization, and if after consultation with the first Member State, they are unable to reach bilateral agreement, the matter will be referred for an arbitration at Community level.

The centralized procedure will be compulsory, in the first instance, for medicinal products derived from biotechnology and veterinary medicines intended for growth or yield promotion purposes, but also available, as an option, for other high technology medicinal products and new chemical entities.

1.4. The reinforced CPMP/CVMP

So far as the mechanism for evaluating applications for authorization is concerned, it appears clear that the Community will have to draw heavily on the resources and experience existing within the Member States. It does not appear feasible to create a complex set of new and independant structures at Community level to duplicate those existing at national level. Rather the aim should be the creation of a technical and administrative secretariat with the necessary resources to coordinate and avoid duplication of existing efforts. In short, the primary emphasis should be on a pooling of resources at Community level, rather than establishing a massive European Drug Administration.

In practical terms, this means that the primary responsibility for the evaluation of applications will remain with the Committee for Proprietary Medicinal Products and the Committee for Veterinary Medicinal Products, albeit with increased resources and responsibilities. In the case of the decentralized procedure it appears that the primary task of the two Committees will remain, as now, the resolution of disagreements which have arisen during the examination of applications for authorization at national level, with important difference that the opinions of the two Committees will also be addressed to the Community institutions for the adoption of binding decisions at the Community level.

In the case of applications submitted through the centralized procedure, it appears essential that the two Committees be given the capacity to undertake a single evaluation of new applications which will be accepted throughout the Community, because only in this way can the waste of resources resulting from parallel evaluation of applications be avoided. Because of the limited expertise available, the actual evaluation of applications will usually be undertaken by the same rapporteurs who have so far undertaken such evaluations on behalf of the Member States. The evaluation will be subjected to a system of peer review within specialist working parties before submission to the Committees for the adoption of a formal opinion. In the new system however, the rapporteurs will have to be selected by the CPMP or the CVMP from among panels of experts and rapporteurs designated by the national competent authorities, and will work on behalf of the Community as a whole.

1.5. The need for an Agency

The progressive introduction of the two new Community authorization procedures will result in a very substantial increase in the workload of the CPMP/CVMP, which are likely to undergo major changes over the next few years. If the two Committees are to be able to function effectively and with proper coordination between them, it is essential that they be given the proper logistical support and resources to make the new procedures work. After considerable reflection, the Commission has concluded that for managerial and budgetary reasons these functions would be undertaken better within an independent European Agency for the Evaluation of Medicinal Products rather than within the Commision itself.

First, it is important to emphasize the sheer scale of the task of evaluating applications for new high technology medicinal products. A typical application for authorization for an innovatory medicine costs in the region of 100 million ECU to prepare and runs to tens of thousands of pages. Although the detailed evaluation of each application will be undertaken by a small number of highly qualified rapporteurs working on behalf of the Community, the logistics involved in preparing assessment reports, summaries of product characteristics and labelling and patient leaflets for 12 Member States are considerable.

Moreover, the authorization of medicinal products is not a once and for all process. Manufacturers are constantly changing the formulation of their products in order to try to improve them, and also seek to amend the terms of an indication, in order to allow the use of the product for new therapeutic indications. It has been estimated that on average two applications are made each year to amend or vary the terms of each marketing authorization. This implies that within a relatively short period of time, the workload involved in managing existing Community authorizations will exceed the workload of assessing new applications for authorization.

In addition to the workload resulting from applications by the pharmaceutical industry to amend the terms of an authorization, account must also be taken of the continuing supervision of the manufacturer by the regulatory authorities, in particular through the monitoring of adverse reaction reports, and inspections and controls of manufacturers. Particularly, in the case of the centralized system, arrangements must be made for the proper exercise and coordination of these responsibilities at the Community level, which implies a need for substantial resources.

For the reasons noted below, it is difficult at the present time to assess in detail the likely workload which will result from the introduction of the new procedures. It is therefore important to ensure that the administrative arrangements which are adopted are sufficiently flexible to allow for the rapid recruitment and redeployment of personnel, as a function of need.

Finally, it is interesting to note that within the Member States the evaluation of medicinal products is frequently entrusted to agencies or institutes which are themselves autonomous of the organs of the central government. The Commission considers that the arguments which have led Member States to take this course of action are also valid for the Community.

The existence at Community level of high-level independent expertise, due to an improved cooperation between competent authorities after the setting-up of the Agency, is an important contribution to the reinforcement of consumer confidence in marketing authorizations granted for human or veterinary medicinal products.

2. THE AUTHORIZATION OF MEDICINAL PRODUCTS AFTER 1992

As noted above, there will be three procedures for the authorization of medicinal products after 1992: decentralized and centralized Community procedures and national registration procedures.

2.1. The decentralized procedure (see table 1)

The decentralized procedure is based upon the principle of mutual recognition of national authorizations, but with important safeguard clauses to allow for the public health issues raised by the authorization of medicinal products, whether human or veterinary. The proposals for the decentralized procedure take account of the experience acquired under the multi-State procedure established by Directive 83/570/EEC and of the more limited experience acquired in the authorization of veterinary medicinal products under Directive 81/851/EEC. In addition, the Commission has decided to try to ensure that the decentralized procedure is as simple and flexible as possible in order to facilitate progressive access to a Community scale market for small and medium sized companies. Unlike the existing Community procedures, there is therefore no minimum threshold number of Member States nor is there any restriction on the number of times the procedure may be used in respect of the same product.

In order to use the decentralized procedure, the company concerned must first submit an application for authorization to one or more Member States in accordance with the current requirements laid down by Community legislation. The reasons for which companies will be permitted to submit this initial application to more than one Member State are further discussed in section 2.2 below. The Member State(s) concerned examine the application in accordance with the normal procedures currently used and decide whether or not to grant authorization. Before granting authorization for any new medicinal product, each Member State will be required to prepare a detailed assessment report for the product concerned, and approve the technical summary of product characteristics (SPC) proposed by the applicant together with the text of the labelling and the patient information leaflet (package insert).

When a company applies for recognition of the initial authorization by one or more of the other Member States of the Community, it will have to submit an identical application to that accepted by the first Member State, including the same application dossier, the same summary of product characteristics and the same formulation and trade mark, unless there are objectively justified reasons for a difference. In addition the other Member State(s) concerned will receive the assessment report directly from the authorities of the first Member State to authorize the product.

In accordance with the principle of mutual recognition, the countries concerned by the decentralized application should usually recognise the authorization granted by the first Member State within a period of 90 days. However, a series of safeguard clauses will allow Member States to oppose mutual recognition if they consider that the medicinal product concerned presents risks to public health.

In this case, the Member State concerned will be expected to forward its own assessment report of the product, together with the reasons for its objections to the first Member State, the other Member States concerned by the application and the applicant. There then follows a period of 60 days which is allowed for bilateral/multilateral discussion of the application between the rapporteurs and co-rapporteurs of the Member States concerned and the applicant in order to try to find an acceptable solution to the problem. Only if it is not possible to reach a solution during this phase is the matter referred through the Agency to the CPMP or the CVMP for an opinion.

In this case, the rapporteur from the first Member State to authorize the product and the co-rapportuers from the other Member States concerned will present an agreed statement of the issues involved, and submit all their assessment reports to the Agency. In addition, the applicant will be required to submit a full copy of the application to the Agency. As appropriate, the CPMP/CVMP will nominate experts to consider the outstanding objections and review the draft summary of product characteristics, the labelling and package insert and the various assessment reports. The conclusions of these experts would then as appropriate be submitted to the various expert panels before submission to the CPMP/CVMP for the adoption of an opinion. This opinion would become binding for the Member States concerned following the regulatory mechanism outlined in section 2.4. However, it should be noted that the final decision at the end of the decentralized procedure will be binding only on those Member States concerned by the application, and will not prevent another Member State from subsequently raising additional objections to the product.

2.2. Relationship between the decentralized procedure and national authorization procedures

One of the more difficult questions to arise during the consultation process concerned the relationship between the existing national authorization procedures and the new Community decentralized procedure, in particular, whether it should be possible for companies to continue to submit parallel applications to two or more Member States for independant assessment after 1992.

After careful consideration the Commission has concluded that during the initial phase of the decentralized procedure, before any Member State has authorized the product, it would be appropriate to continue to allow companies to submit applications in parallel to two or more of the Member States. In practice, to limit the industry to choosing only one Member State for the initial application would give that country an unacceptable unilateral power of decision on the access of a product to the Community market. Moreover, in principle it appears desirable to encourage a degree of competition between the regulatory authorities of the Member States.

However, the possibility of submitting parallel applications is subject to two important restrictions.

First, with effect from 1993 onwards, where a Member State is aware that another Member State is undertaking a detailed evaluation of the medicinal product concerned, it will be able to suspend its own evaluation and wait for the detailed assessment report from the other Member State. This provision will provide the Member States with a means of eliminating any unnecessary duplication of effort and waste of scarce scientific resources.

Second, from 1996 onwards, it will no longer be possible to pursue parallel applications after one Member State has authorized the product concerned. Once the first authorization is granted, all other pending applications will automatically be transformed into applications for mutual recognition under the decentralized procedure, thus guaranteeing uniform decisions throughout the internal market.

It follows that after 1996, national registration procedures will be limited to the initial phase of the decentralized procedure, and for purely local products which are not intended for export to any other Member State.

These transitional arrangements are necessary in order to ensure that the Agency can take up its responsibilities on a progressive basis, and to avoid any unnecessary disruption to current registration procedures while the new Community procedures are being phased in.

2.3. The centralized procedure (Table II)

The proposals for the new centralized Community authorization procedure take into account the practical experience acquired during the operation of the existing procedures established for biotechnology-high technology medicinal products established by Directive 87/22/EEC.

The use of the procedure will be compulsory for the vast majority of medicinal products derived from biotechnology, listed in Part A of the Annex to the regulation. In addition, in a new departure, the use of the centralized procedure will also be compulsory for veterinary medicinal products which are intended to increase the productivity of food-producting animals, because of the specific Community interest which these products represent.

In addition, the procedure will be available on an optional basis for other high-technology medicinal products listed in Part B of the Annex, and, in a further new departure, to other products containing a new chemical entitity.

These restrictions on the scope of the centralized procedure appear necessary in the first instance to ensure the progressive establishment of the Agency and a smooth transfer of responsibilities from the Member States to the Community. The scope of the centralized procedure will be reviewed in the light of experience in 1998-99, when the possibility of extending it to other categories of products, either on an optional or a compulsory basis, will be reconsidered.

Applications for authorization will be submitted directly to the Agency. The exact form of the application, together with such practical information as the fees payable, linguistic requirements, and the presentation of the information will be set out in a Notice to Applicants to be prepared by the Agency.

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The application will then be referred to the CPMP or the CVMP as appropriate for review. For each application a rapporteur will be appointed to undertake overall responsibility for the coordination of the review of the product, and experts will be appointed to assist the rapporteur in the evaluation of individual parts of the file. These rapporteurs and experts will be appointed by the Committee responsible, from lists of experts provided by the Member States. They will however report directly to the Committee and not to their individual national authorities.

Working under the supervision of the CPMP/CVMP and consulting its expert advisory panels as appropriate, the task of the rapporteur will be to prepare an assessment report for the product concerned, and to review the draft summary of product characteristics and the labelling and package inserts for the medicinal product concerned proposed by the applicant.

These drafts will then be presented to the CPMP/CVMP for its scientific opinion, which will become binding following the regulatory mechanism described in section 2.4.

The overall time allowed for the preparation of the opinion of the Agency by the relevant committee is 210 days, although this would be suspended by any time allowed to the applicant to reply to questions posed by the Committee.

2.4. The mechanism for binding Community decisions

In accordance with the principles underlying the Community treaties, the tasks of the new Agency are purely advisory, and it is neither possible or appropriate to delegate to the Agency the power to take decisions on the authorization of new medicinal products which would be binding on the Community and the Member States. Such decisions can only be taken by the existing Community institutions.

In proposing a mechanism for the adoption of binding decisions on the authorization of medicinal products within the Community, the Commission has sought to ensure that, as far as possible, decisions are taken on the basis of the objective scientific criteria of quality, safety and efficacy. It was also thought important to protect the integrity of the Agency by ensuring that all questions of a scientific nature are resolved within the Agency structure and are not subject to a second review during the decision-making process. In addition consideration has to be given to the very large number of decisions likely to be required, probably well in excess of 500 per year by 2000, particularly when decisions on variations and amendments to existing authorizations are taken into consideration.

At the conclusion of its evaluation the CPMP/CVMP will forward to the Commission, to the Member States and the applicant its opinion consisting of:

- the assessment report on the product, and in the event of a favourable opinion;
- the summary of product characteristics, in all nine Community languages;
- the labelling and package insert for the product, also in nine languages.

Following receipt of the opinion, the Commission will have 30 days to prepare a draft of the decision to be taken. In the vast majority of cases this draft will reflect the scientific opinion transmitted by the Agency. Because of its general obligation to supervise the legality of all the work undertaken by the Agency taking into consideration the objectives of Community policies, the Commission must reserve the right in exceptional circumstances, not to follow the opinion. In such cases, however, the Commission will have to provide detailed reasons for not following the opinion.

The draft decision will be circulated to all Member States and to the applicant. The Member States will have 30 days to submit detailed written reasons explaining any objections to the draft decision. If no objections are received within the 30 day timelimit, the Commission will adopt the decision to grant or refuse a European marketing authorization.

If objections are received, the Commission will have to consider, in consultation with the staff of the Agency, whether these objections raise new scientific issues which have not yet been fully explored within the relevant Committee. If this is the case, the Commission will refer the application back to the Agency with a request that the Committee concerned reconsider its opinion within a 60 day period.

However, should it appear that all the scientific issues have been adequately addressed, the Commission will refer the draft for a decision to be taken on the basis of a qualified majority vote within the Standing Committee on Medicinal Products for Human Use or the Standing Committee on Veterinary Medicinal Products using the so-called 'regulatory committee procedure' (variant 3a of Council Decision 87/373/EEC of 13 July 1987 laying down the procedures for the exercise of implementing powers conferred upon the Commission).

2.5. Transparency of administrative procedures

At the present time, the Community pharmaceutical directives already contain several provisions designed to ensure the transparency authorization procedures for medicinal products. In particular, the authorities are required to give detailed reasons for all negative decisions, to grant appeal rights and to publish decisions. These requirements will also apply to both Community registration procedures.

During the decentralized procedure, applicants will be given the right to participate in discussions between the Member States during the bilateral phase. In both the centralized and decentralized procedures they will have the right to submit oral or written responses to questions posed by the CPMP/CVMP during the evaluation of the product, and a formal right of appeal prior to the transmission of the opinion of the Agency to the Member States and to the Commission. The applicant may also be given an opportunity to make representations to the regulatory Committee, at the discretion of that Committee.

In addition, applicants will, of course have the formal rights of redress against acts of the Commission or the Council conferred by Articles 173, 175 and 215 of the EEC Treaty.

In addition to the appeal rights given to pharmaceutical companies, efforts are also being made to increase the openness of the authorization process for the general public. It is envisaged that the assessment reports prepared by the Agency will be made available to the public, if necessary after editiong to remove any commercially confidential information. Moreover, the Agency will be under a general obligation to develop appropriate contacts with the general public and consumer, patient and professional representatives.

2.6. Status of marketing authorizations

a) European Marketing Authorizations

European marketing authorizations which have been granted following the centralized procedures will apply throughout the Community, and have the same status in each Member State as marketing authorizations granted in accordance with national procedures. They will apply for five years, renewable on application at least three months in advance. European marketing authorizations may be amended only by the Commission, after the opinion of the CPMP/CVMP has been obtained, in accordance with the procedures described above.

Although in principle a Community marketing authorization based on the criteria of quality, safety and efficacy will be valid throughout the Community, there are occasional circumstances which may justify restrictions on the use of a medicinal product which satisfy these criteria.

In the case of medicinal products for human use, it is proposed to include in the basic Directive 65/65/EEC an Article to enable Member States to prohibit the use of a product on their territory for objectively defined reasons of public order or public policy. Such a provision appears necessary, in particular, in order to take account of the rather different policies of the Member States in relation to birth control. However, Member States will be obliged to inform the Commission whenever this exception is invoked, and the Commission will be able to intervene in cases of abuse.

The use of immunological veterinary medicinal products may also present certain difficulties resulting from differences in animal disease status within the different regions of the Community. In order not to interfere with the operation of disease eradication programmes, it is necessary to enable the Member States to prohibit the use of certain types of vaccines on all or part of their territory, notwithstanding that they satisfy the criteria for authorization, and are in fact used in other regions of the Community.

Moreover, within the veterinary medicines sector, the grant of a European Marketing Authorization will in no way effect the operation of particular legislation prohibiting or restricting the use of certain types of veterinary medicine, resulting from the objectives of the Common Agricultural Policy.

In exceptional cases, where there is a serious new risk to public health, a Member State may impose temporary restrictions on the use of a product covered by a European marketing authorization provided that the CPMP/CVMP and the Commission are informed of the measure and the detailed reasons for it, at the latest on the working day following the imposition of the measure. The CPMP/CVMP will be required to consider urgently the measures taken by the Member States and to give its opinion on them. The CPMP/CVMP opinion will be circulated to the Commission, the Member States and the person responsible for marketing in accordance with the procedures described above, but with shorter time limits to take account of the urgency. The Member State which has adopted temporary measures may maintain them in force until such time as a definitive decision is adopted.

b) Acceptance of national authorizations

Where authorizations have been accepted following the decentralized procedure, with or without referal to the CPMP/CVMP, the responsibility for the management of the authorization will lie with the Member State which first authorized the product. All relevant pharmacovigilance data shall be submitted to that authority for consideration with a copy to all other Member States concerned. All proposals to amend the terms of a marketing authorization shall be submitted to the Member State which first authorized the product. The decision of that Member State will be notified to all the Member States which have accepted the authorization. In the event of objections (which remain unresolved even after multi-lateral discussions) from the other Member States about possible amendments to the terms of a marketing authorization, the matter will be referred to the CPMP/CVMP for arbitration.

c) National procedures after 1992

The facility of purely national authorization procedures will remain for companies too small to avail themselves of the internal market, and for products of local interest. The procedures for granting marketing authorization will remain unchanged.

In the case of products authorized before 1993, the Member States will remain responsible for the management of authorizations. However, the Member States and the Commission will continue to have the right to request an application to be examined by the reinforced CPMP/CVMP in specific cases where the interests of the Community are involved, particularly when divergent decisions have been made (Directive 75/319/EEC as modified, Articles 11 and 12).

3. EUROPEAN PHARMACOVIGILANCE

The term "Pharmacovigilance" is meant to cover the collection of information on adverse drug reactions (ADRs), at pre-and post- marketing stage, the scientific evaluation of these ADR reports and the regulatory decisions which may have to be taken following their analysis. These regulatory decisions may include in extreme cases withdrawal or suspension of the marketing authorization, but, more often, a modification of the legal status of the drug and amendments or warnings in the summary of products characteristics, labelling and package leaflet.

3.1. Pharmacovigilance experience in the EEC

Pharmacovigilance is a major issue for the current functioning of the CPMP or the CVMP, as well as for any future system of authorization of medicinal products in Europe.

Arising from its mandate under Directive 75/319/EEC, and its public health responsibility, the CPMP has for many years been concerned with issues of pharmacovigilance. The original system of routine discussion at meetings and manual exchange of data has been superseeded by a number of innovations, namely:

- a rapid alert system using fast communication methods;
- a drug information monitor which identifies selected products and updates the information at each CPMP meeting;
- pharmacovigilance hearings with companies, followed by CPMP pharmacovigilance opinions;
- standardization of summary of product characteristics for products of significant Community interest.

In December 1988, the Commission circulated to the Member States a detailed questionnaire relating to their pharmacovigilance system. The Commission issued thereafter, in September 1989, a report on the present situation of pharmacovigilance in the European Community (III/3577/89). Furthermore, in 1989, the Commission has, in consultation with the CPMP, established an ad hoc Pharmacovigilance working party, which meets in parallel with the CPMP. This new working party has two essential advisory roles to the Commission and the CPMP, first on general questions of pharmacovigilance methodology, second to assist the CPMP for the scientific evaluation of ADR data related to specific medicinal products.

During the last 12 months, the CPMP has exchanged pharmacovigilance information on 30 medicinal products. Since July 1986, the CPMP has adopted 6 formal pharmacovigilance opinions.

In the veterinary medicines sector, increasing importance is being attached to that question, and the CVMP has recently established its own working party to exchange information and try to harmonize methodology on pharmacovigilance questions.

3.2. ADR reporting

The legal status, requirements and structure of national pharmacovigilance systems vary considerably throughout the Community. Besides spontaneous pharmacovigilance, there are several types of structured pharmacovigilance, based on the recruitement of physicians for the monitoring of specific medicinal products. In this context, it should be noted that, in addition to spontaneous pharmacovigilance, three Member States may require by law that pharmacovigilance be a condition for the granting of a marketing authorization.

In most of the Member States, reporting by the medical veterinary profession(s) and by pharmacists is voluntary. For routine reporting by companies a 6 month frequency is the emerging pattern. For serious ADRs, time limits and frequency of reporting vary. Where reporting is mandatory, sanctions may be taken for not doing so. Causality is either assessed by expert judgement alone (staff of the centres, expert panels and committees) or in combination with an algorithm. The body reviewing information has access to the marketing authorization dossier. Member States do not systematically relate adverse drug reactions to data on drug usage. This can however be done in cases of concern.

Experience has shown that pharmacovigilance centres should be situated as close as possible to the source of the reports. As far as spontaneous ADR reports are concerned, regional or national centres will remain the most important link between the source of the report and any Community coordination system of pharmacovigilance.

3.3. Future obligations on pharmaceutical companies

The authorization holder will be required to ensure that the authority which granted the authorization is informed of any serious adverse drug reaction resulting from the use of a medicinal product in humans or animals in accordance with the terms of the authorization. Such information shall be communicated by the company within 15 days of receipt. The authorization holder shall have permanently his own pharmacovigilance contact point, responsible for:

- the organization and maintainence of a system for collecting adverse reaction data, from whatever source, and the maintenance of a register of all reported ADRs.
- supplying all relevant information to the competent authorities in the Community regarding the benefit/risk assessment including information on the volume of sales or prescription as well as reports on ADRs occurring outside the European Community;
- preparation and submission of regular reports to the authority which authorized the medicinal product; (e.g. every 6 months during the first two years of marketing and annually for the next three years).
- the preparation and submission of post-marketing studies, when these are required as a condition of the authorization.

3.4. An increasing role for the Community

Each Member State will required to designate a national center as a contact point for the Community. National or Regional centres should be established for the collection of ADRs and the evaluation of both spontaneous reports and reports submitted by the holders of marketing authorization. Companies should be notified by the national center of all spontaneous reports they receive, and should be given a possibility to comment on them.

The technical aspect of the exchange of information between Member States as well as the causality assessment method should preferably be harmonized at Community level. Systems utilized by WHO or CIOMS should normally be adopted by the Community pharmacovigilance network. As from 1993, pharmacovigilance data will have to be evaluated with a view to harmonizing decisions and actions applicable in all the Member States. The EEC pharmacovigilance network is thus clearly not intended to replace neither the national nor the WHO system, but to optimize and harmonize pharmacovigilance activities in the EEC. When required under Directive 89/341/EEC, the Community will also bring to the attention information which may affect the protection of public health in third countries via the World Health Organization.

Current experience in the CPMP shows that pharmacovigilance information is sometimes transmitted too late, when a national decision has already been taken. Community legislation should provide for regular transmission of evaluated data and for immediate transmission by the national centres of all information on serious ADRs. A routine information exchange, e.g. covering alerts on non-serious ADRs and the rapid alert system would continue to run in parallel. The rapid alert system, recently implemented, will have to be improved, using electronic mail. A pharmacovigilance information should be considered as an alert if, in case of confirmation, it implies the modifications of the conditions of marketing authorization. In order not to overload the system, only laerts concerning serious ADRs should be transmitted via the "Rapid Alert System".

The legal obligations of the Member States, which are currently set out in Articles 30 and 33 of Directive 75/319/EEC and Articles 39 and 42 of Directive 81/851/EEC, have been reviewed in the context of the two Community procedures. The nature and frequency of the information transmitted to the reinforced CPMP/CVMP structure has been better defined. Any decision made at Community level on the basis of a CPMP pharmacovigilance opinion should be preceded by an appropriate consultation with the concerned companies.

4. SUPERVISION AND SANCTIONS

4.1. Access to inspection reports

The rapporteurs for the application will, where necessary, be able to request a copy of the most recent inspection report covering the manufacturer concerned, for decentralized and centralized applications.

Where a manufacturer is established in a third country, appropriate multi-lateral arrangements will also have to be made to ensure that the rapporteurs working on behalf of the CPMP/CVMP have access to inspection reports and other relevant documents, in the same way as rapporteurs currently working for the individual Member States.

During its evaluation of a live rDNA vaccine, manufactured in a third country, the CVMP considered that an inspection of the manufacturing plant was desireable in order to verify the guarantees offered relating to the quality and safety of the product concerned. During discussions on the proposal to extend the veterinary medicines directives to cover immunological products, the Council has also requested that arrangements should be made to enable coordinated inspections of manufacturers in third countries to be undertaken on behalf of the Community in appropriate cases.

It has therefore appeared necessary to include within the administrative structure of the Agency a responsibility for coordinating the discharge of the various inspection functions of the Member States, both within the Community and in third countries.

4.2. Supervision of manufacturers, withdrawal of authorization and sanctions

In accordance with the general principles laid down in the Community pharmaceutical directives, the primary responsibility for the supervision of manufacturers lies with the competent authorities of the Member State in which the manufacturer is established. In the case of products imported from third countries, this responsibility will lie on the authorities of the Member State where the tests and controls necessary on importation are carried out, unless an appropriate arrangement has been made between the Community and the third country concerned to ensure that the product is manufactured in accordance with Community requirements and the necessary controls are conducted in the third country. In case of doubt, provision is made for coordinated inspections using inspectors from two or more Member States or inspectors employed by the Agency.

The grounds for the suspension or withdrawal of a European marketing authorization are the same as for the suspension or withdrawal of a national authorization. However, a European authorization can be withdrawn only by the Community, following the opinion of the Agency and the application of the procedures described in section 2.4. In case of urgency, however, a Member State would be able to temporarily suspend the use of a medicinal product, provided that the matter was immediately referred to the Commission for application of the Community procedures.

In addition to withdrawal of the marketing authorization, certain forms of misconduct may expose the authorization holder or the applicant to criminal or administrative sanctions, in accordance with the law of the member State concerned. Since there is no specific Community penal law, a clause has been included which makes misconduct by the applicant for or holder of a European marketing authorization liable to the same penalties as the holder of a national authorization in the Member State concerned.

5. THE EUROPEAN AGENCY FOR THE EVALUATION OF MEDICINAL PRODUCTS

The establishment of a new European Agency for the evaluation of medicinal products will be essential in order to enable the Community institutions to discharge the major new responsibilities imposed upon them as a result of the introduction of the new Community authorization procedures and the additional responsibilities in the field of pharmacovigilance and the supervision of manufacturers.

In the early years, the establishment of the Agency will inevitably result in a significant increase in the overall level of public expenditures associated with the authorization and supervision of medicinal products. In order to ensure the orderly phasing in of the new Community procedures alongside national procedures, some degree of duplication will be necessary at first. However, in the longer term the pooling of resources at Community level and the elimination of wasteful duplication of effort in the evaluation of medicinal products will result in significant reductions in the overall cost to society of authorizing and supervising medicinal products through reduced expenditures at national level.

In all Member States, the costs of registering pharmaceutical products are met in part from fees paid by the pharmaceutical industry. However, in most Member States, these fees are paid into the general national budget and are not specifically devoted to the costs of the authorization system. It is therefore difficult to know what proportion of the cost of the system is met by fees. Moreover, in the case of medicinal products for human use, this question is to some extent academic, since the costs of fees are undoubtedly passed on to the consumer/patient, and, therefore frequently met by the State under the national health insurance system.

For the introduction of the future system, the Commission considers that those costs which are directly attributable to the evaluation of applications for authorization of new medicinal products should be covered by fees from the pharmaceutical industry. On the other hand, the general activities undertaken by the Agency in respect of pharmacovigilance, the provision of information about medicinal products, inspection and standards should be financed by a general contribution from the Community budget, under a new budgetary line to be created in the operations part of the budget. Given the difficulty of making precise estimates of the workload of the Agency, at least in the early years, the exact fee structure will be determined by a special financial regulation, to be adopted following consultation of the pharmaceutical industry.

5.1. Functions of the Agency

Under the direct supervision of the CPMP/CVMP, placed at the top of its scientific structures, the European Medicines Agency will be responsible for:

- the coordination of the evaluation, on a scientific basis, of the quality, safety and efficacy of medicinal products which are submitted in accordance with Community authorization procedures;
- the production of evaluation reports, summaries of product characteristics and labelling and package inserts for these medicinal products;
- the continuing supervision of medicinal products authorized for use within the Community, and the provision of advice on appropriate regulatory action to be taken in respect of such products;
- coordinating the exercise by the Community and the Member States of the various supervisory responsibilities concerning the manufacture and testing of medicinal products, including GMPs, GLPs, GCPs, batch controls etc;
- advising the Member States and the Community institutions on all questions relating to medicinal products;
- advising on maximum residue levels for veterinary medicines.

3)

The Agency will also be responsible for promoting better cooperation between public control laboratories (collaborative tests, methods and reference preparations) in close cooperation with the European Pharmacopoeia. Furthermore, the Agency should become an interface between national pharmacovigilance centres throughout the Community.

5.2. Structure of the Agency

Besides its scientific committees at the top of the structure (CPMP/CVMP), the Agency shall have an executive director, who will report to an administrative board.

a) Scientific bodies: CPMP, CVMP and Scientific Council

The examination of scientific questions submitted to the Agency for opinion will be the responsibility of:

- the Committee for Proprietary Medicinal Products, for medicinal products for use in humans;
- the Committee for Veterinary Medicinal Products, for medicinal products for veterinary use.

Both Committees will consist of scientific advisors nominated by Member States and meet every month/2 months. These Committees may request the establishment of specialised working parties and panels of experts to assist in the evaluation of scientific questions submitted to the Agency for opinion. In order to assist the Agency in the exercise of its responsibilities, the Member States will communicate to the Agency and maintain up-to-date lists of experts with particular competence in the various areas of the evaluation of medicinal products. The services of experts will be performed on the basis of mandates which will be confered onto them by the CPMP/CVMP. They will be reimbursed by the Agency, in accordance with a scale to be fixed by Council regulation for the various tasks involved.

In order to maintain high scientific standards in the operations of the Agency, the CPMP and CVMP should have the possibility to take advice from a high level Scientific Council of 5 personalities of international repute (Nobel prize etc.) nominated by the Council of Ministers upon proposal from the Commission. This Council would meet once or twice a year to deal with difficult ethical or scientific questions referred to it by the CPMP/CVMP and to evaluate globaly the scientific statements of the Agency.

b) Administrative board

The administrative board will consist of two representatives from each Member State and of the Commission. One representative will be specifically responsible for matters relating to medicinal products for human use and one for veterinary medicinal products. The mandate of the representatives shall be for three years, renewable. The administrative board will elect its president for a period of three years and shall adopt its own internal rules of procedure. Each member of the administrative board will have one vote. The decisions of the administrative board will be adopted by a two-thirds majority of its members. The secretariat of the administrative board will be provided by the Agency. Each year the administrative board will adopt:

- the report of activities for the past year
- the programme of work for the following year
- the draft annual accounts for the past year
- the draft estimate of income and expenditure for the following year.

c) Secretariat of the Agency

An executive director in charge of the secretariat of the Agency, will be nominated by Council, upon a proposal from the Commission, for a renewable period of five years. The executive director will be the legal representative of the Agency, responsible for:

- the routine administration of the Agency
- the preparation of the income and expenditure report, and the administration of the budget of the Agency
- all matters relating to the personnel of the administrative and technical secretariat.

The technical and administrative staff of the Agency will be responsible for providing all necessary logistical support for the CPMP and the CVMP, and for assisting in the discharge of the various responsibilities of the Agency as described in section 5.1.

5.3. Finance and Resources

a) Estimated Workload

The establishment of an administrative and technical secretariat will be progressive, based initially on the anticipated workload. In the medium term, the reallocation of workload via the reinforced CPMP/CVMP will globally tend to reduce the workload of the 12 competent authorities.

The CPMP has done a survey (III/1625/88) estimating the average number of first applications for NCE products (new chemical entities) in the Community as 50 per annum. Of these, approximately 20% could be considered as high tech. For each NCE the rate is approximately 6 variations in the first five years. Industry sources have confirmed these figures. From the experience of the concertation procedure, it would be reasonable to project approximately 15 new High tech/biotech applications a year, with at least a similar rate of variations as for NCE's. As the secretariat would also assist the reinforced CPMPin its role as a forum of arbitration in the decentralized procedure, the number of referrals must be estimated. With the opportunity of a Single Internal Market, the number of applications through the decentralized procedure is likely to increase dramatically. Already now, the mult-state procedure is showing a 60% annual increase in applications (1988 = 31; 1989 = 50). Currently, all applications are referred to the CPMP. Thus a workload of at least 150 dossiers for human medicines a year could be anticipated after 1992.

So far as veterinary medicines are concerned, initially much of the workload for the reinforced CVMP will result from the setting up of a centralized Community procedure for the establishment of maximum residue levels. Over the period 1993-1997, the toxicology data for approximately 150 compounds will have to be reviewed. Since it is intended that from 1992 onwards, all applications for NCE's intended for use in food-producting animals will be submitted to a centralized Community procedure for the determination of maximum residue level, it may be that there will also be a greater take up of the centralized procedure for applications for marketing authorization. It is therefore prudent to estimate that 10 applications for NCE's will be referred to the centralized procedure, together with 5 biotech applications, making 15 in total. In addition, approximately 25 referrals a year could be expected initially under the decentralized procedure, although this could rise very substantially should the decentralized procedure prove an attractive option for extending the terms of existing authorization into minor species.

b) Resources

The responsibilities of the Agency and it's permanent secretariat will encompass a range of activities. In estimating personnel resource requirements, the following functions must be considered.

- management of the dossiers, including validation of European dossiers and variations;
- administration of the reinforced CPMP/CVMP;
- administrative and technical support of the reinforced CPMP/CVMP, its working parties and expert panels;
- administrative operation of expert groups, contracts etc;
- coordination of pharmacovigilance activities;
- establishment of veterinary residue limits;
- implementation of Community certification procedures in the areas of GMP, GCP, GLP etc.;
- support for the pharmaceutical data bank;
- personnel and administration (interpretation and translation, legal, accountancy and informatics, archives and publications, etc.).

The number of meetings, meeting rooms and facilities would relate to workload but a core requirement would be:

- 2 meetings per annum of the administrative board;
- 1 meeting per month of the 2 scientific committees (CPMP/CVMP) ;
- panel meetings of rapporteurs and experts to assess an application (experts released for week long meetings);
- working party meetings of experts (8 W.P. x 4 times per annum);
- ad hoc meetings of particular scientific experts and drafting groups (for example, 5 experts, 15 meetings per year).

Estimates of the necessary resources are set out in the financial statement annexed to this proposal.

6. OTHER AMENDMENTS TO COMMUNITY PHARMACEUTICAL LEGISLATION

In addition to the incidental changes to the existing directives relating to human and veterinary medicinal products resulting from the establishment of the new Community registration procedures, several other detailed changes to the legislation are also proposed.

6.1. Timelimit for the evaluation of applications by Member States

The timelimit of 120 days, plus a further 90 days in exceptional circumstances, allowed for the evaluation of applications by Member States was first laid down in 1965. However, since that time, the amount of information to be provided in an application and its complexity has increased substantially. In practice, all Member States are finding it increasingly difficult, if not impossible to meet their obligations under Community Law in this respect, and a period of 210 days has become the general rule. The Commission is therefore proposing to extend the period allowed for review by Member States to 210 days. However, in return, the Commission will expect the Member States to respect these new deadlines scrupulously, and reserves the right to institute proceedings under Article 169 of the Treaty against any Member State which does not comply with the new time limits.

6.2. Environmental assessment

In view of the increasing awareness of the effects of medicinal products on the environment, the Commission is proposing that in appropriate cases an application for authorization for a medicinal product for human use include an assessment of the potential risks presented by the product for the environment. The details of the information required will be specified in the Annex to Directive 75/318/EEC on the testing requirements for medicinal products for human use.

So far as veterinary medicinal products are concerned, similar provisions have already been proposed by the Commission and are currently under consideration by the Council (COM (88) 779 final).

So far as live vaccines containing genetically modified organisms are concerned, Council Directive 90/220/EEC of 23 April 1990 shall apply (O.J. N° L 117 of 8.5.90).

6.3. Imports from third countries

Proposals are included to ensure that medicinal products imported from third countries are manufactured in accordance with standards of good manufacturing practice at least equivalent to those laid down by the Community.

6.4. Conditional marketing authorizations

At the present time, the directives relating to human and veterinary medicines do not make any express provision for conditions to be attached to a marketing authorization, such as a requirement to conduct further studies after authorization. However, experience has shown that Phase IV studies, which are conducted in patients after authorization of the product, and under practical conditions of use may provide information which is valuable for re-evaluating the overall benefits and risks of an individual medicinal product. It is therefore proposed that it should be possible to attach such conditions to the terms of a national or European marketing authorization for a medicinal product for human or veterinary use.

7. SPECIAL PROVISIONS FOR VETERINARY MEDICINAL PRODUCTS

7.1. Residues

In February 1989, the Commission presented proposals for laying down Community procedures for the establishment of maximum residue levels for residues of veterinary medicines in foods. These proposals are currently under consideration in the Council, and it is therefore necessary to consider the relationship between the proposed procedure for the establishment of MRLs with the new Community authorization procedures provided for by the present proposals.

In recent years some concern has been expressed by consumers that foodstuffs from animals which are used in clinical trials of veterinary medicines are being sold for human consumption, thereby exposing the consumer to residues of experimental substances whose properties are not fully known.

However, for economic reasons, it is often impossible to run large-scale trials involving hundreds or thousands of animals unless it is possible to sell the animals for human consumption.

In practice, all Member States have developed national systems for monitoring the conduct of clinical trials in animals and for removing any risk to the consumer. In order to provide equivalent guarantees at the Community level, the Commission is proposing that it should not be permitted to let foodstuffs from trial animals enter the human food chain unless the safety of the compound concerned has been evaluated at the Community level and residues have been found to be without risk for public health.

In the case of other categories of veterinary medicinal product, it will be up to the manufacturer to decide whether to submit the application for the establishment of a maximum residue level before the submission of the application of authorization, or at the same time.

7.2. Link between the veterinary medicines legislation and the feed additives Directives

For historical reasons, a number of pharmacologically active compounds are authorized for use in the Community as additives to animal feedingstuffs under Directive 70/524/EEC rather than as veterinary medicinal products. In accordance with Directive 70/524/EEC, a decision on the transfer of the coccidiostats and other medicinal substances from that Directive to the veterinary medicines directives shall be taken once the level of harmonization in the veterinary medicines sector has attained that applicable to additives.

The introduction of the new Community procedures provided for by these proposals will undoubtedly be a major factor in this respect. However, a number of other difficult questions will need to be resolved, in particular whether the authorizations under Directive 70/524/EEC, which are granted by substance, should be converted into European marketing authorizations, which are granted for individual products produced by specific manufacturers.

In any case, it is essential to ensure that any transfer of these products from one regulatory regime to the other does not result in any lowering of the level of harmonization already achieved, any reduction in the level of protection of health or any disruption for the manufacturers of the products concerned.

For these reasons, the Commission is not proposing the immediate transfer of these compounds. Instead, the Commission is proposing that a full report on the issues raised by the transfer should be presented within three years of the entry into force of the new system in order to enable the Council to take a decision in full knowledge of the facts.

8. FINAL REMARKS

In accordance with the provisions of Articles 8A and 8C of the Treaty establishing the European Economic Community, the Commission requests the member States to take the measures necessary to comply with this package of proposals by 1 January 1993.

The Commission has taken into account the requirements of Article 8C of the Treaty and has concluded that no special provision seems to be justified at this stage.

The Commission has also studied the question of the high levels of health, safety, environmental and consumer protection equired by the terms of Article 100 A, paragraph 3. It has done so following consultation of the industrial and social partners concerned, and in the light of an analysis of the risks inherent in this area and of the current technical capabilities of the European industry. The proposals take full account of these considerations in the light of the overall objectives of this provision of the Treaty.

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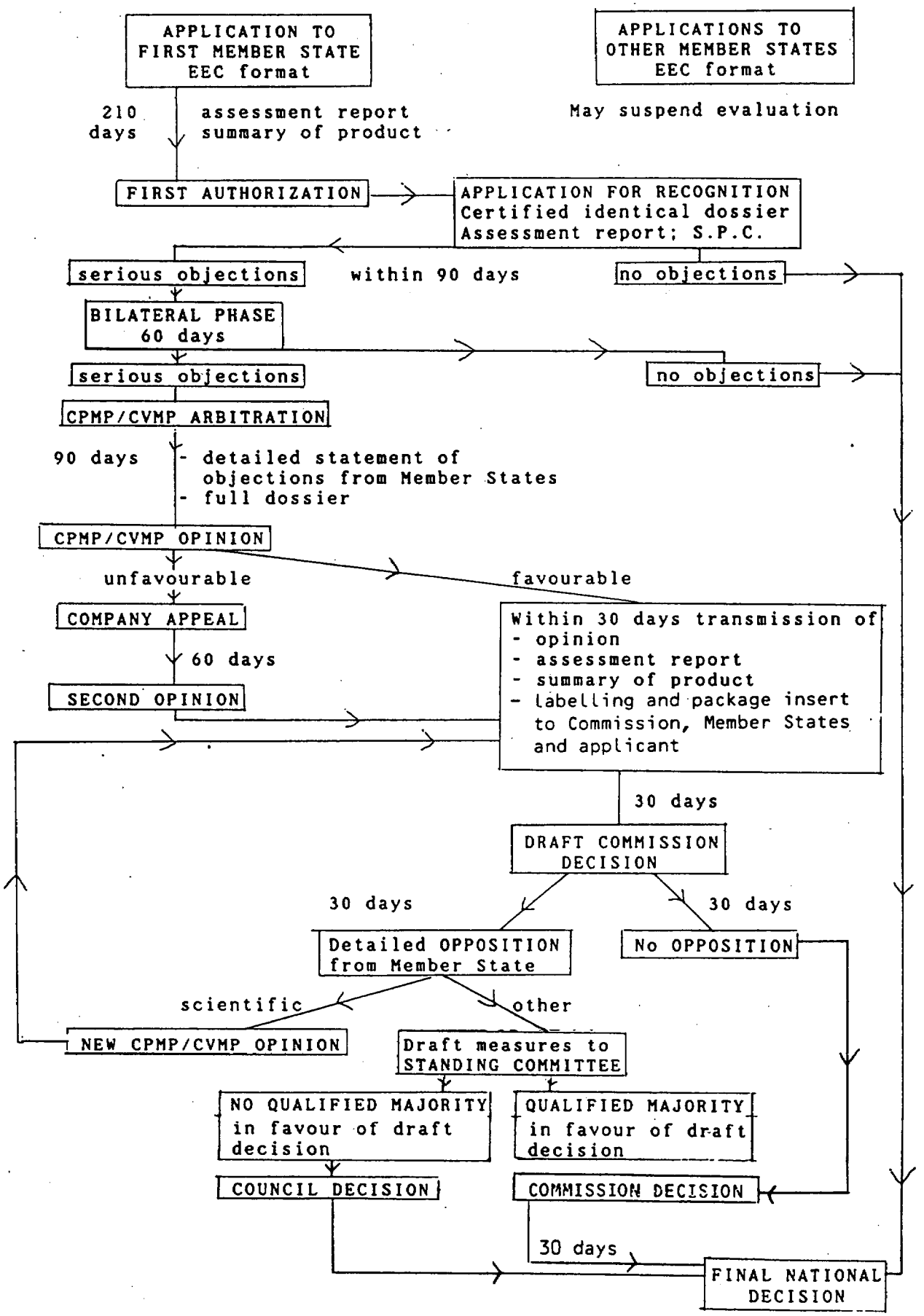


TABLE II: CENTRALIZED PROCEDURE

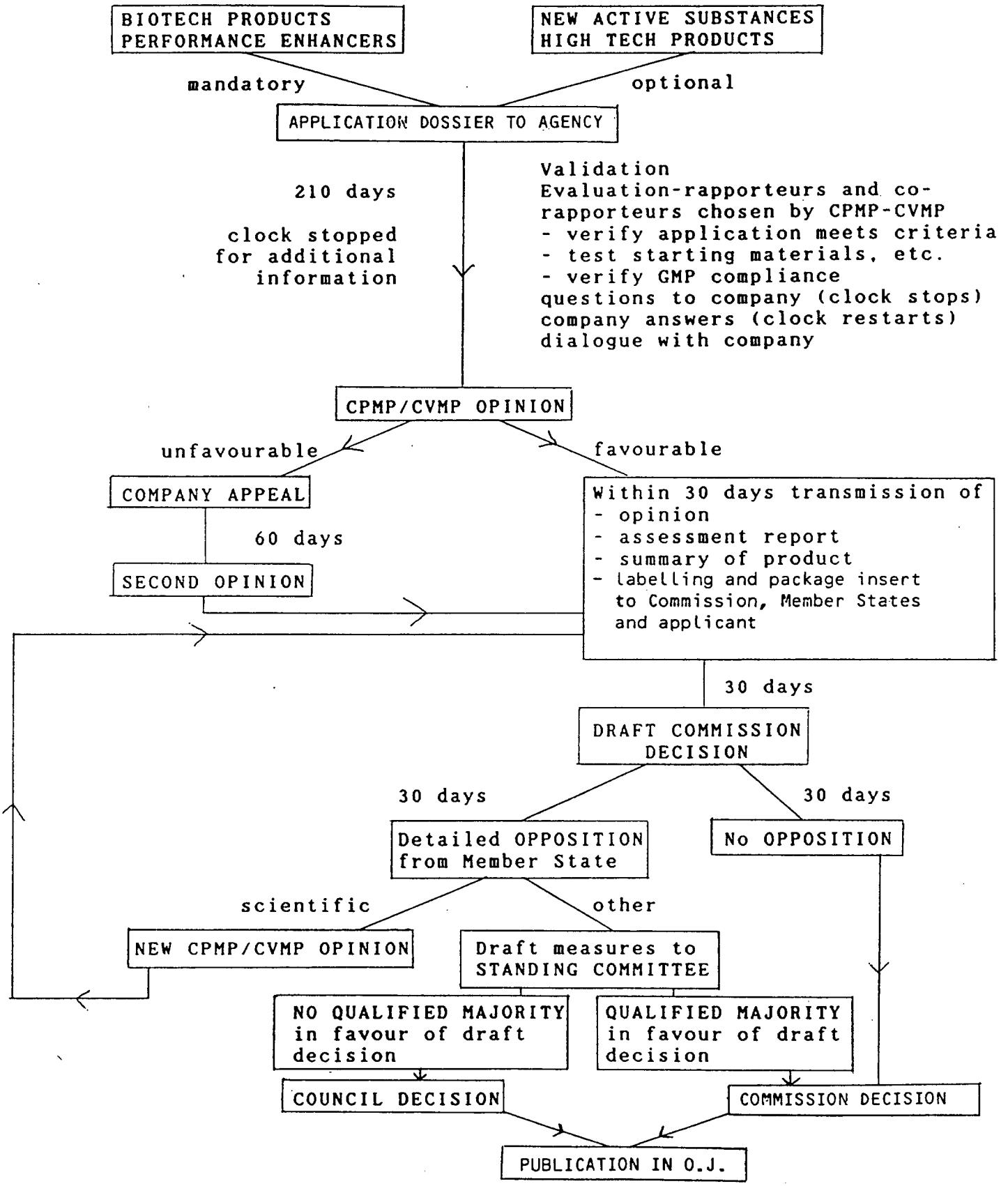
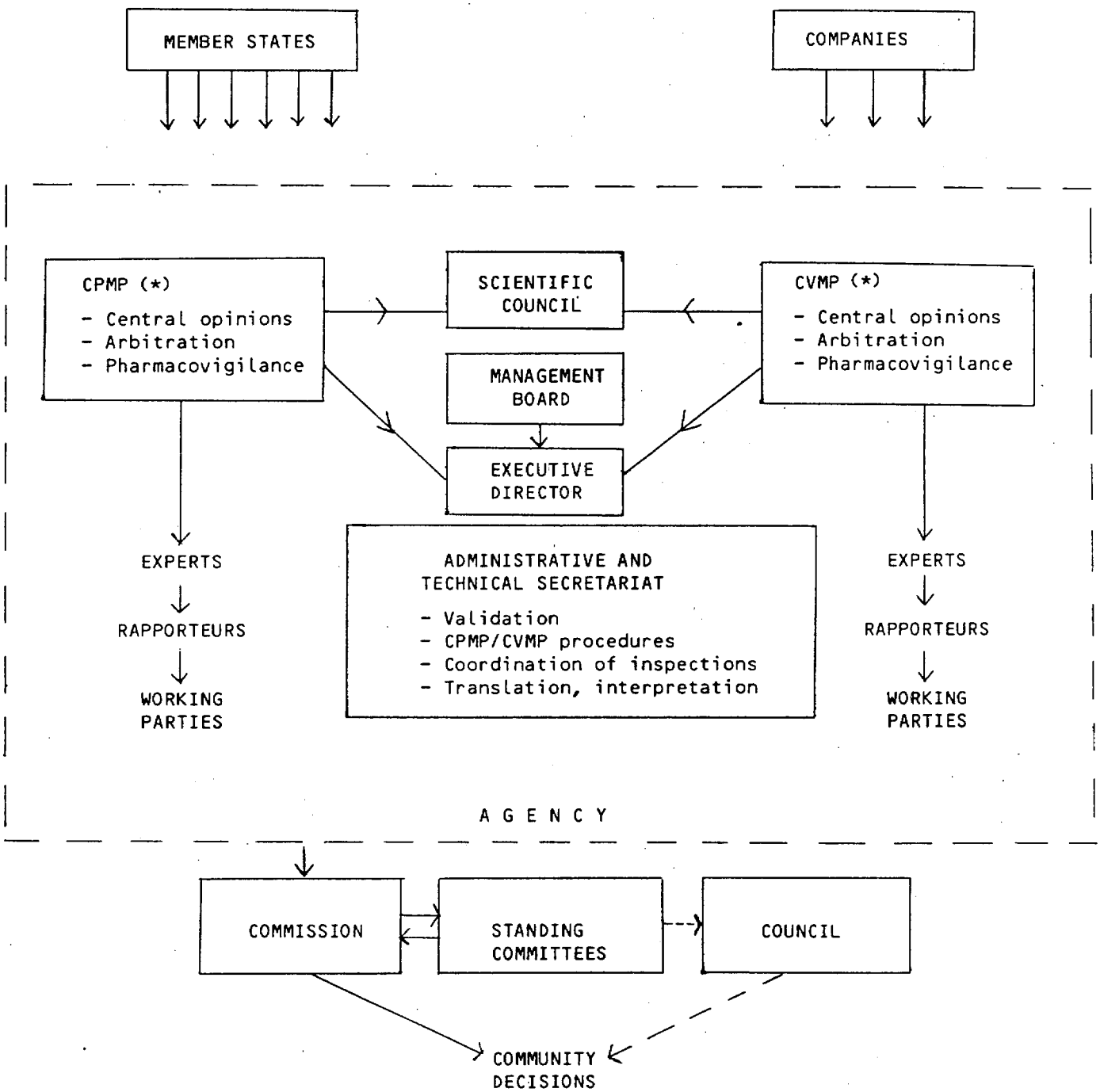


TABLE III: THE EUROPEAN AGENCY FOR THE EVALUATION OF MEDICINAL PRODUCTS



(*) CPMP = Committee for Proprietary Medicinal Products
CVMP = Committee for Veterinary Medicinal Products

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1. Decentralized procedure

General References: Directive 75/319/EEC, Chapter III
Directive 81/851/EEC, Chapter IV

	75/319	81/851
Filing of application	9(1)	17(1)
Information for Committee	9(2)	17(2)
Information for Member State of origin	9(3)	17(3)
Obligation to recognize authorization	9(4)	17(4)
Grounds for refusing to recognize	10(1)	18(1)
Bi-multilateral phase	10(2)	18(2)
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- representations to regulatory committee	14(4)	22(4)
Phasing in of decentralized procedure	65/65	81/851
- information about applications in other Member States	4(11)	5(13)
- compulsory assessment reports	4b	5b
- possibility to suspend evaluation	7(2)	8(2)
- use of decentralized procedure to be systematic for applications involving more than one Member State from 1.1.96	7a	8a

2. Other changes to national procedures	65/65	81/851
210 days for evaluation	7(1)	8(1)
Need to consider safety in the environment	4(6a)	N/A
Manufacturing process to be updated	9b	14b
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PROPOSAL FOR A COUNCIL REGULATION (EEC)

laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products

Proposal for a

COUNCIL REGULATION (EEC)

laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community, and in particular Article 100a thereof;

Having regard to the proposal from the Commission(1),

In cooperation with the European Parliament(2),

Having regard to the opinion of the Economic and Social Committee(3),

Whereas it is important to adopt measures with the aim of progressively establishing the internal market over a period expiring on 31 December 1992; whereas the internal market shall comprise an area without internal frontiers in which the free movement of goods, persons, services and capital is ensured;

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(1)

(2)

(3)

Whereas Council Directive 87/22/EEC of 22 December 1986 on the approximation of national measures relating to the placing on the market of high technology medicinal products particularly those derived from biotechnology [4] has established a Community mechanism for concertation, prior to any national decision relating to a high-technology medicinal product, with a view to arriving at uniform decisions throughout the Community;

Whereas the experience acquired as a result of Directive 87/22/EEC has shown that it is necessary to establish a centralized Community authorization procedure for technologically advanced medicinal products, in particular those derived from biotechnology; whereas this procedure should also be available to persons responsible for marketing medicinal products containing new active substances which are intended for use in human beings or in food producing-animals;

Whereas in the interests of public health it is necessary that decisions on the authorization of such medicinal products should be based on the objective scientific criteria of the quality, the safety and the efficacy of the medicinal product concerned to the exclusion of economic or other considerations; whereas, however, Member States should exceptionally be able to prohibit the use on their territory of medicinal products for human use which infringe objectively defined concepts of public order or public morality; whereas moreover a veterinary medicinal product may not be authorized by the Community if its use would contravene the rules and objectives laid down by the Community within the framework of the Common Agricultural Policy;

(4) OJ No L 15, 17.1.87, p. 38.

Whereas, in the case of medicinal products for human use, the criteria of quality, safety and efficacy have been extensively harmonized by Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products[5], as last amended by Directive .../.../EEC[6] and Second Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation and administrative action relating to proprietary medicinal products[7] as last amended by Directive ../.../EEC[8], and by Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of the Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of medicinal products[9] as last amended by Directive ../.../EEC[10];

Whereas in the case of veterinary medicinal products, the same results have been achieved by Council Directive 81/851/EEC of 28 September 1981 on the approximation of the laws of the Member States relating to veterinary medicinal products[11] as last amended by Directive ../.../EEC[12] and by Council Directive 81/852/EEC of 28 September 1981 on the approximation of the laws of the Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of veterinary medicinal products[13] as last amended by Directive ../.../EEC[14];

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(5) OJ No 22, 9.2.65, p. 369/65.

(6)

(7) OJ No L 147, 9.6.75, p. 13.

(8)

(9) OJ No L 147, 9.6.75, p. 13.

(10)

(11) OJ No L 317, 6.11.81, p. 1.

(12)

(13) OJ No L 317, 6.11.81, p. 16.

(14)

Whereas the same criteria must be applied to medicinal products which are to be authorized by the Community;

Whereas only after a single scientific evaluation of the highest possible quality of all the benefits and risks of technologically advanced medicinal products, should a marketing authorization be granted by the Community by a rapid procedure ensuring close cooperation between the Commission and Member States;

Whereas Council Directive ../.../EEC has provided that in the event of a disagreement between Member States about the quality, safety or efficacy of a medicinal product which is the subject of the decentralized Community authorization procedure, the matter should be resolved by a binding Community decision following a scientific evaluation of the issues involved within a European Medicines Evaluation Agency; whereas similar provisions have been laid down in respect of veterinary medicinal products by Council Directive ../.../EEC;

Whereas the Community must be provided with the means to undertake a scientific evaluation of medicinal products which are presented for authorization in accordance with the centralized Community procedures; whereas, furthermore, in order to achieve the effective harmonization of the administrative decisions taken by Member States in relation to individual medicinal products which are presented for authorization in accordance with decentralized procedures, it is necessary to provide the Community with a means of resolving disagreements between Member States about the quality, safety and efficacy of medicinal products;

Whereas it is therefore necessary to establish a European Agency for the Evaluation of Medicinal Products ("the Agency");

Whereas the primary task of the Agency should be to provide scientific advice of the highest possible quality to the Community institutions and the Member States for the exercise of the powers conferred upon them by Community legislation in the field of medicinal products in relation to the authorization and supervision of medicinal products;

Whereas it is desirable to ensure close cooperation between the Agency and scientists working within the Member States;

Whereas, therefore, the exclusive responsibility for preparing the opinions of the Agency on all matters relating to medicinal products for human use should be entrusted to the Committee for Proprietary Medicinal Products created by Second Council Directive 75/319/EEC; whereas, in respect of veterinary medicinal products this responsibility should be entrusted to the Committee for Veterinary Medicinal Products created by Council Directive 81/851/EEC;

Whereas the establishment of the Agency will make it possible to reinforce the scientific role and independence of these two Committees, in particular through the establishment of a permanent technical and administrative secretariat;

Whereas each Committee should be able to request the opinion of a Scientific Council consisting of scientists of internationally recognised standing on difficult questions of a general scientific or ethical nature relating to the authorization of medicinal products;

Whereas it is also necessary to make provision for the supervision of medicinal products which have been authorized by the Community, and in particular for the intensive monitoring of adverse reactions to those medicinal products through Community pharmacovigilance activities in order to ensure the rapid withdrawal from the market of any medicinal product which presents an unacceptable level of risk under normal conditions of use;

Whereas the Agency, working in close cooperation with the Commission, should also be entrusted with the task of coordinating the discharge of the various supervisory responsibilities of Member States and in particular monitoring the respect of good manufacturing practices, good laboratory practices and good clinical practices;

Whereas it is necessary to provide for the orderly introduction of Community procedures for the authorization of medicinal products alongside the national procedures of the Member States which have already been extensively harmonized by Directives 65/65/EEC, 75/319/EEC and 81/851/EEC; whereas it is therefore appropriate in the first instance to limit the obligation to use the new Community procedure to medicinal products which are produced by means of specified biotechnological processes, and to make the procedure available on an optional basis only to high-technology medicinal products and to medicinal products containing totally new active substances; whereas the scope of the Community procedures should be reviewed in the light of experience at the latest six years after the entry into force of this Regulation;

HAS ADOPTED THIS REGULATION:

TITLE I

DEFINITIONS AND SCOPE

Article 1

The objective of this regulation is to lay down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and to establish a European Agency for the Evaluation of Medicinal Products.

Article 2

The definitions laid down in Article 1 of Directive 65/65/EEC and the definitions laid down in Article 1 paragraph 2 of Directive 81/851/EEC shall apply to this Regulation.

Article 3

1. No medicinal product which is referred to in Part A of the Annex shall be placed on the market within the Community unless authorization has been granted by the Community in accordance with the provisions of this Regulation.

2. The person responsible for marketing a medicinal product referred to in Part B of the Annex may request that authorization to place the medicinal product on the market be granted by the Community in accordance with the provisions of this Regulation.

Article 4

1. In order to obtain the authorization referred to in Article 3, the person responsible for marketing shall submit an application to the European Agency for the Evaluation of Medicinal Products, hereinafter referred to as "the Agency".

2. The Community shall issue and supervise authorizations to place medicinal products for human use on the market in accordance with Title 2.

3. The Community shall issue and supervise authorizations to place veterinary medicinal products on the market in accordance with Title 3.

TITLE 2

AUTHORIZATION AND SUPERVISION OF MEDICINAL PRODUCTS FOR HUMAN USE

CHAPTER 1

Submission and examination of applications - authorizations - renewal of authorization

Article 5

The Committee for Proprietary Medicinal Products established by Article 8 of Directive 75/319/EEC, in this title referred to as "the Committee", shall be responsible for formulating the opinion of the Agency on any question relating to the grant, amendment, suspension or withdrawal of an authorization to place a medicinal product for human use on the market arising in accordance with the provisions of this Regulation.

Article 6

1. An application for authorization for a medicinal product for human use shall be accompanied by the particulars and documents referred to in Articles 4 and 4a of Directive 65/65/EEC and Article 2 of Directive 75/319/EEC.

2. The application shall also be accompanied by the fee payable to the Agency for the examination of the application.

3. The Agency shall ensure that the opinion of the Committee is given within 210 days of the receipt of a valid application.

4. The Agency shall, in consultation with Member States, the Commission and interested parties, draw up detailed guidance on the form in which applications for authorization are to be presented.

Article 7

In order to prepare its opinion, the Committee:

a) shall verify that the particulars and documents submitted in accordance with Article 6 comply with the requirements of Directives 65/65/EEC, 75/318/EEC and 75/319/EEC, and examine whether the conditions for issuing an authorization to place the medicinal product on the market specified in this Regulation are satisfied;

b) may request a laboratory designated for this purpose to test the medicinal product, its starting materials, and if need be, its intermediate products or other constituent materials in order to ensure that the control methods employed by the manufacturer and described in the application documents are satisfactory;

c) may, where appropriate, request the applicant to supplement the particulars accompanying the application. Where the Committee avails itself of this option, the time limit laid down in Article 6 shall be suspended until such time as the supplementary information requested has been provided. Likewise, this time limit shall be suspended for the time allowed to the applicant to prepare oral or written explanations.

Article 8

1. Upon receipt of a written request from the Committee, a Member State shall forward the information necessary to verify that the manufacturer of a medicinal product or the importer from a third country is able to manufacture the medicinal product concerned and/or carry out the necessary control tests in accordance with the particulars and documents supplied in accordance with Article 6.

2. Where it considers it necessary in order to complete its examination of an application, the Committee may request the applicant to submit to an inspection of the manufacturing site of the medicinal product concerned. The inspection, which shall be completed within the time limit referred to in Article 6, shall be undertaken by qualified pharmaceutical inspectors from the Member States who may, if appropriate, be accompanied by an inspector from the Agency.

Article 9

1. Where the opinion of the Committee is that:
   - the application does not satisfy the criteria for authorization set out in this Regulation, or
   - the summary of product characteristics proposed by the applicant in accordance with Article 6 should be amended, or
   - the labelling or package insert of the product is not in compliance with Directive ../../EEC, or
   - the authorization should be granted subject to the conditions provided for in Article 13(2)

   the Agency shall forthwith inform the applicant.

   Within 15 days of the receipt of the opinion, the applicant may provide written notice to the Agency that he wishes to appeal. Within 60 days of the receipt of the grounds for appeal, the Committee shall consider whether its opinion should be revised, and the reasons for the conclusions reached on the appeal shall be annexed to the assessment report referred to in paragraph 2.

2. Within 30 days of its adoption, the Agency shall forward the final 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.

3. In the event of an opinion in favour of granting authorization to market the medicinal product concerned, the following documents shall be annexed to the opinion:

a) a draft summary of the product characteristics, as referred to in Article 4a of Directive 65/65/EEC;

b) details of any conditions or restrictions which should be imposed on the supply or use of the medicinal product concerned, including the conditions under which the medicinal product may be made available to patients, having regard to the criteria laid down in Council Directive ../.../EEC [concerning the legal status for the supply of medicinal products for human use];

c) the draft text of the labelling and package leaflet proposed by the applicant, presented in accordance with Council Directive ../.../.. [on the labelling of medicinal products for human use and on package leaflets].

Article 10

1. Within 30 days of the receipt of the opinion, the Commission shall prepare a draft of the Decision to be taken in respect of the application, taking into account the objectives of Community policies and considering all the relevant information. In the event of a draft Decision which envisages the granting of a marketing authorization, the documents referred to in points (a), (b) and (c) of paragraph 3 of Article 9 shall be annexed. The Commission shall transmit the draft Decision to the Member States and to the applicant.

The Commission shall explain in detail the reasons for any differences between the draft Decision and the opinion of the Committee.

2. The Commission shall adopt the Decision to be taken in respect of the application unless, within 30 days, it has received a reasoned request from a Member State to reconsider the matter. The Member State concerned shall also transmit a copy of its request to the other Member States and the applicant within the same time limit.

3. Within the time limit referred to in paragraph 2, the applicant may submit written observations on the draft Decision for consideration by the Commission.

4. The Commission shall examine any reasoned request received in accordance with paragraph 2, in consultation with the Agency, and after consideration of any further observations submitted by the applicant.

   If the Commission considers that the request raises questions of a scientific or technical nature requiring further examination, it may remit the matter to the Agency. In this case the Committee shall give a second opinion within a time limit of 60 days. Within 30 days of the receipt of the opinion, the Commission shall adopt the Decision to be taken in respect of the application.

   Otherwise the Decision shall be taken in accordance with the procedure laid down in Article 2b and 2c of Directive 75/318/EEC.

Article 11

Without prejudice to other provisions of Community law, the authorization provided for in Article 3 shall be refused if, after verification of the information and particulars submitted in accordance with Article 6, it appears that the quality, the safety or the efficacy of the medicinal product have not been adequately demonstrated by the applicant.

Authorization shall likewise be refused if the particulars and documents provided by the applicant in acordance with Article 6 of this Regulation are incorrect or if the labelling and package leaflets proposed by the applicant are not in accordance with Directive ../.../...

Article 12

1. Without prejudice to Article 6 of Directive 65/65/EEC, a marketing authorization which has been granted in accordance with the procedure laid down in this Regulation shall apply throughout the Community. It shall confer the same rights and obligations in each of the Member States as a marketing authorization granted by that Member State in accordance with Article 3 of Directive 65/65/EEC.

2. The refusal of a Community marketing authorization shall constitute a prohibition on the marketing of the medicinal product concerned throughout the Community.

3. An announcement that authorization has been granted shall be published for information purposes in the Official Journal of the European Communities.

4. Upon request from any interested person, the Agency shall make available a detailed summary of the evaluation of the medicinal product by the Committee and the reasons for its opinion in favour of granting authorization after deletion of any information of a commercially confidential nature.

Article 13

1. Authorization shall be valid for five years and shall be renewable for five year periods, on application by the holder at least three months before the expiry date.

2. In exceptional circumstances and following consultation with the applicant, an authorization may be granted subject to such conditions as appear necessary to ensure the protection of public health, including specific obligations to conduct further studies following the granting of authorization and specific obligations in respect of the reporting of adverse reactions to the medicinal product.

3. Medicinal products which have been authorized by the Community in accordance with the provisions of this Regulation 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.

Article 14

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

CHAPTER 2

Supervision and sanctions

Article 15

1. After an authorization has been issued, the person responsible for placing the medicinal product on the market must, in respect of the methods of production and control provided for in points 4 and 7 of the second paragraph of Article 4 of Directive 65/65/EEC, take account of technical and scientific progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods. These changes must be approved in accordance with this Regulation.

2. The person responsible for marketing shall forthwith inform the Agency of any new information which might entail the amendment of the particulars and documents referred to in Article 6 or in the approved summary of the product characteristics. In particular the person responsible for marketing shall forthwith inform the Agency of any prohibition or restriction imposed by the competent authorities of any country in which the medicinal product is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product concerned.

3. If the person responsible for marketing proposes to make any alteration to the information and particulars referred to in Article 6, he shall submit an application to the Agency.

4. The Agency shall, in consultation with the Commission, adopt appropriate arrangements for the examination of amendments and variations to the terms of a marketing authorization.

Article 16

When a marketing authorization is granted in accordance with this regulation, one or more of the Member States shall act as the competent supervisory authorities to exercise the responsibilities referred to in Article 17.

In the case of medicinal products manufactured within the Community, the supervisory authorities shall normally be the competent authorities of the Member State or Member States which have granted the manufacturing authorization provided for in Article 16 of Directive 75/319/EEC in respect of the manufacture of the medicinal product concerned.

In the case of medicinal products imported from third countries, the supervisory authorities shall be the competent authorities of the Member States in which the controls referred to in Article 22 (1) (b) of Directive 75/319/EEC are carried out unless appropriate arrangements have been made between the Community and the exporting country to ensure that those controls are carried out in the exporting country and that the manufacturer applies standards of good manufacturing practice at least equivalent to those laid down by the Community.

Article 17

1. The supervisory authorities shall have responsibility for verifying on behalf of the Community that the manufacturer or the importer from third countries satisfies the requirements laid down in Chapter IV of Directive 75/319/EEC, and for exercising supervision over persons responsible for marketing medicinal products in accordance with Chapter V of Directive 75/319/EEC.

2. Upon receipt of a reasoned request by any Member State, or on its own initiative, the Commission may request the manufacturer or importer to submit to an inspection of the manufacturing site of the medicinal product concerned, giving its reasons. The inspection shall be undertaken by qualified pharmaceutical inspectors from the Member States who may, if appropriate, be accompanied by an inspector from the Agency. The report of the inspectors shall be made available to the Commission, the Committee and the applicant. In the case of an inspection conducted within the Community, the host Member State shall provide all the practical support necessary to enable the inspectors to discharge their responsibilities.

Article 18

1. Where the supervisory authorities or the competent authorities of any other Member State are of the opinion that the manufacturer or importer from third countries is no longer fulfilling the obligations laid down in Chapter IV of Directive 75/319/EEC, they shall forthwith inform the Committee and the Commission, stating their reasons in detail and indicating the course of action proposed.

   The same shall apply where a Member State considers that one of the measures envisaged in Chapter V of Directive 75/319/EEC should be applied in respect of the medicinal product concerned.

2. The Commission shall in consultation with the Agency forthwith examine the reasons advanced by the Member State concerned. It may request the opinion of the Committee within a time limit to be determined by the Commission having regard to the urgency of the matter. Whenever practicable, the person responsible for marketing shall be invited to provide oral or written explanations.

3. The Commission shall prepare a draft of the Decision to be taken which shall be adopted in accordance with the procedure laid down in Article 10.

However, where a Member State has invoked the provisions of paragraph 4, the time limit provided for in Article 2 c, paragraph 3 of Directive 75/318/EEC shall be reduced to 15 calendar days.

4. In exceptional cases, where action is urgently necessary to protect public health, a Member State may suspend the use on its territory of a medicinal product which has been authorized in accordance with this Regulation. It shall inform the Commission no later than the following working day of the reasons for its action. The Commission shall immediately consider the reasons given by the Member State in accordance with paragraph 2 and shall initiate the procedure provided for in paragraph 3.

5. A Member State which has adopted the suspensive measures referred to in paragraph 4 may maintain them in force until such time as a definitive Decision has been reached in accordance with the procedure laid down in paragraph 3.

CHAPTER 3

Pharmacovigilance

Article 19

For the purpose of this Chapter, the definitions given in Article 29b of Directive 75/319/EEC shall apply.

Article 20

The Agency, acting in close cooperation with the national pharmacovigilance centres established in accordance with Article 29a of Directive 75/319/EEC, shall be responsible for the collection and evaluation of information about adverse reactions to medicinal products which have been authorized by the Community in accordance with this Regulation.

The competent authorities of the Member States and the person responsible for marketing shall ensure that all relevant information about adverse reactions to medicinal products authorized in accordance with this Regulation are brought to the attention of the Agency in accordance with the provisions of this Regulation.

Article 21

The person responsible for marketing a medicinal product authorized by the Community in accordance with the provisions of this Regulation shall have permanently and continuously at his disposal a person responsible for pharmacovigilance. This person shall be responsible for:

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

b) the preparation and submission of the reports referred to in Article 22 to the competent authorities of the Member States and the Agency in accordance with the requirements of this Regulation;

c) ensuring that any request for the provision of additional information necessary for the evaluation of the benefits and risks of a medicinal product is answered fully and promptly, including the provision of information about the volume of sales or prescriptions for the medicinal product concerned where relevant.

Article 22

1. The person responsible for marketing shall ensure that all suspected serious adverse reactions to a medicinal product authorized in accordance with the provisions of this Regulation which are brought to his attention by a qualified health care professional, whether arising within the Community or a third country, are recorded and reported to the Agency within 15 days.

2. In addition, the person responsible for marketing shall be required to maintain detailed records of all other adverse reactions arising within the Community which are reported to him by a qualified health care professional. Unless other requirements have been laid down as a condition of the granting of authorization by the Community, these records shall be submitted to the Agency immediately upon request or at least every six months during the first two years following authorization and once a year for the following three years. Thereafter, the records shall be submitted at five yearly intervals together with the application for renewal of the authorization, or immediately upon request.

Article 23

Each Member State shall report any suspected serious adverse reaction arising within its territory to a medicinal product authorized in accordance with this Regulation to the Agency and the person responsible for marketing within 15 days of receipt of a report from a qualified health care professional.

Article 24

The Agency shall, in consultation with Member States, the Commission and interested parties, draw up detailed guidance on the collection, verification and presentation of adverse reaction reports.

Article 25

1. The Agency shall publish an annual report on the operation of the procedures laid down in this Chapter.

2. Within six years of the entry into force of this Regulation, the Commission shall publish a detailed review of the operation of the procedures laid down in this Chapter and shall propose any amendments which may be necessary to improve the operation of these procedures.

   The Council shall decide on the Commission proposal within one year.

TITLE 3

AUTHORIZATION AND SUPERVISION OF VETERINARY MEDICINAL PRODUCTS

CHAPTER 1

Submission and examination of applications - authorization - renewal of authorization

Article 26

The Committee for Veterinary Medicinal Products established by Article 16 of Directive 81/851/EEC, in this title referred to as "the Committee", shall be responsible for formulating the opinion of the Agency on any question relating to the grant, amendment, suspension or withdrawal of an authorization to place a veterinary medicinal product on the market arising in accordance with the provisions of this Regulation.

Article 27

1. An application for authorziation for a veterinary medicinal product shall be accompanied by the particulars and documents referred to in Articles 5, 5a and 7 of Directive 81/851/EEC.

2. The application shall also be accompanied by the fee payable to the Agency for the examination of the application.

3. The Agency shall ensure that the opinion of the Committee is given within 210 days of the receipt of a valid application.

4. The Agency shall, in consultation with Member States, the Commission and interested parties, draw up detailed guidance on the form in which applications for authorization are to be presented.

Article 28

In order to prepare its opinion, the Committee:

a) shall verify that the particulars and documents submitted in accordance with Article 27 comply with the requirements of Directives 81/851/EEC and 81/852/EEC, and examine whether the conditions for issuing an authorization to place the veterinary medicinal product on the market specified in this Regulation are satisfied;

b) may request a laboratory designated for this purpose to test the veterinary medicinal product, its starting materials, and if need be, its intermediate products or other constituent materials in order to ensure that the control methods employed by the manufacturer and described in the application documents are satisfactory;

c) may request a laboratory designated for this purpose to verify, using samples provided by the applicant, that the analytical detection method proposed by the applicant in accordance with point 8 of the second paragraph of Article 5 of Directive 81/851/EEC is suitable for use in routine checks to reveal the presence of residue levels above the maximum residue level accepted by the Community in accordance with the provisions of Council Regulation (EEC) No 2377/90 of 26 June 1990 laying down a Community procedure for the establishment of maximum residue levels for veterinary medicinal products(15);

d) may, where appropriate, request the applicant to supplement the particulars accompanying the application. Where the Committee avails itself of this option, the time limit laid down in Article 28 shall be suspended until such time as the supplementary information requested has been provided. Likewise, this time limit shall be suspended for the time allowed to the applicant to prepare oral or written explanations.

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(15) OJ No L 224, 18.8.1990, p. 1.

Article 29

1. Upon receipt of a written request from the Committee, a Member State shall forward the information necessary to verify 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 in accordance with Article 27.

2. Where it considers it necessary in order to complete its examination of an application, the Committee may request the applicant to submit to an inspection of the manufacturing site of the veterinary medicinal product concerned. The inspection, which shall be completed within the time limit referred to in Article 27, shall be undertaken by qualified pharmaceutical inspectors from the Member States, who may, if appropriate be accompanied by an inspector from the Agency.

Article 30

1. Where the opinion of the Committee is that:
   - the application does not satisfy the criteria for authorization set out in this Regulation, or
   - the summary of product characteristics proposed by the applicant in accordance with Article 27 should be amended, or
   - the labelling or package insert of the product is not in compliance with Directive 81/851/EEC, or
   - the authorization should granted subject to the conditions provided for in Article 34(2),

   the Agency shall forthwith inform the applicant.

Within 15 days of the receipt of the opinion, the applicant may provide written notice to the Agency that he wishes to appeal. Within 60 days of the receipt of the grounds for appeal, the Committee shall consider whether its opinion should be revised, and the reasons for the conclusions reached on the appeal shall be annexed to the assessment report referred to in paragraph 2.

2. 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 veterinary medicinal product by the Committee and stating the reasons for its conclusions.

3. In the event of an opinion in favour of granting authorization to market the veterinary medicinal product concerned, 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;

b) in the case of a veterinary medicinal product intended for administration for food producing animals, a statement of the maximum residue level which may be accepted by the Community in accordance with Regulation (EEC) .../90;

c) details of any conditions or restrictions which should be imposed on the supply or use of the veterinary medicinal product concerned, including the conditions under which the medicinal product may be made available to users;

d) the draft text of the labelling and package leaflet, proposed by the applicant, presented in accordance with Chapter VII of Directive 81/851/EEC.

Article 31

1. Within 30 days of the receipt of the opinion, the Commission shall prepare a draft of the Decision to be taken in respect of the application taking into account the objectives of Community policies and considering all relevant information. In the event of a draft Decision which envisages the granting of a marketing authorization, the documents referred to in points (a), (b), and (c) of paragraph 3 of Article 30 shall be annexed. The Commission shall transmit the draft Decision to the Member States and to the applicant.

   The Commission shall explain in detail the reasons for any differences between the draft Decision and the opinion of the Committee.

2. The Commission shall adopt the Decision to be taken in respect of the application unless, within 30 days, it has received a reasoned request from a Member State to reconsider the matter. The Member State concerned shall also transmit a copy of its request to the other Member States and the applicant within the same time limit.

3. Within the time limit referred to in paragraph 2, the applicant may submit written observations on the draft Decision for consideration by the Commission.

4. The Commission shall examine any reasoned request received in accordance with paragraph 2, in consultation with the Agency, and after consideration of any further observations submitted by the applicant.

   If the Commission considers that the request raises questions of a scientific or technical nature requiring further examination, it may remit the matter to the Agency. In this case the Committee shall give a second opinion within a time limit of 60 days. Within 30 days of the receipt of the opinion, the Commission shall adopt the Decision to be taken in respect of the application.

   Otherwise the Decision shall be taken in accordance with the procedure laid down in Article 2b and 2c of Directive 81/852/EEC.

Article 32

Without prejudice to other provisions of Community law, the authorization provided for in Article 3 shall be refused if, after verification of the information and particulars submitted in accordance with Article 27, it appears that:

1. the veterinary medicinal product is harmful under the conditions of use stated at the time of the application for authorization, is not efficacious or the applicant has not provided sufficient proof of efficacy as regards the species of animal which is to be treated, or its qualitative and quantitative composition is not as stated;

2. the withdrawal period recommended by the applicant is not long enough to ensure that foodstuffs obtained from treated animals do not contain residues which might constitute a health hazard for the consumer or is insufficiently substantiated;

3. the veterinary medicinal product is offered for sale for a use prohibited under other Community provisions.

Authorization shall likewise be refused if the particulars and documents provided by the applicant in accordance with Article 27 of this Regulation are incorrect or if the labelling and package leaflets proposed by the applicant are not in accordance with Chapter VII of Directive 81/851/EEC.

Article 33

1. Without prejudice to Article 4 of Council Directive ../.../EEC [extending the scope of Directive 81/851/EEC on the approximation of the laws of the Member States relating to veterinary medicinal products], and laying down additional provisions for immunological veterinary medicinal products, a marketing authorization which has been granted in accordance with the procedure laid down in this regulation shall apply throughout the Community. It shall confer the same rights and obligations in each of the Member States as a marketing authorization granted by that Member State in accordance with Article 4 of Directive 81/851/EEC.

2. The refusal of a Community marketing authorization shall constitute a prohibition on the marketing and administration to animals of the veterinary medicinal product concerned throughout the Community.

3. An announcement that authorization has been granted shall be published for information purposes in the Official Journal of the European Communities.

4. Upon request from any interested person, the Agency shall make available a detailed summary of the evaluation of the veterinary medicinal product by the Committee and the reasons for its opinion in favour of granting authorization, after deletion of any information of a commercially confidential nature.

Article 34

1. Authorization shall be valid for five years and shall be renewable for five year periods, on application by the holder at least three months before the expiry date.

2. In exceptional circumstances, and following consultation with the applicant, an authorization may be granted subject to such conditions as appear necessary to ensure the protection of human or animal health, including specific obligations to conduct further studies following the granting of authorization and specific obligations in respect of the reporting of adverse reactions to the veterinary medicinal product.

3. Veterinary medicinal products which have been authorized by the Community in accordance with the provisions of this Regulation shall benefit from the ten year period of protection referred to in point 10 of the second paragraph of Article 5 of Directive 81/851/EEC.

Article 35

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

CHAPTER 2

Supervision and sanctions

Article 36

1. After an authorization has been issued, the person responsible for placing the veterinary medicinal product on the market must, in respect of the methods of production and control provided for in points 4 and 9 of the second paragraph of Article 5 of Directive 81/851/EEC, take account of technical and scientific progress and introduce any changes that may be required to enable the veterinary medicinal product to be manufactured and checked by means of generally accepted scientific methods. These changes must be accepted by the Community.

   Upon request from the Commission, the person responsible for placing the veterinary medicinal product on the market shall also review the analytical detection methods provided for in point 8 of the second paragraph of Article 5 of Directive 81/851/EEC and propose any changes which may be necessary to take account of technical and scientific progress.

2. The person responsible for marketing shall forthwith inform the Agency of any new information which might entail the amendment of the particulars and documents referred to in Article 27 or in the approved summary of the product characteristics. In particular the person responsible for marketing shall forthwith inform the Agency of any prohibition or restriction imposed by the competent authorities of any country in which the veterinary medicinal product is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product concerned.

3. If the person responsible for marketing proposes to make any alteration to the information and particulars referred to in Article 27, he shall submit an application to the Agency.

4. The Agency shall, in consultation with the Commission, adopt appropriate arrangements for the examination of amendments and variations to the terms of a marketing authorization.

Article 37

When a marketing authorization is granted in accordance with this regulation, one or more of the Member States shall act as the competent supervisory authorities to exercise the responsibilities referred to in Article 38.

In the case of veterinary medicinal products manufactured within the Community, the supervisory authorities shall normally be the competent authorities of the Member State or Member States which have granted the manufacturing authorization provided for in Article 24 of Directive 81/851/EEC in respect of the manufacture of the veterinay medicinal product concerned.

In the case of veterinary medicinal products imported from third countries, the supervisory authorities shall be the competent authorities of the Member States in which the controls referred to in Article 30 (1) (b) of Directive 81/851/EEC are carried out unless appropriate arrangements have been made between the Community and the exporting country to ensure that those controls are carried out in the exporting country and that the manufacturer applies standards of good manufacturing practice at least equivalent to those laid down by the Community.

Article 38

1. The supervisory authorities shall have responsibility for verifying on behalf of the Community that the manufacturer or the importer from third countries satisfies the requirements laid down in Chapter V of Directive 81/851/EEC, and for exercising supervision over persons responsible for marketing medicinal products in accordance with Chapter VI of Directive 81/851/EEC.

2. Upon receipt of a reasoned request of any Member State, or on its own initiative, the Commission may request the manufacturer or importer to submit to an inspection of the manufacturing site of the veterinary medicinal product concerned, giving its reasons. The inspection shall be undertaken by qualified pharmaceutical inspectors from the Member States who may, if appropriate, be accompanied by an inspector from the Agency. The report of the inspectors shall be made available to the Commission, the Committee and the applicant. In the case of an inspection conducted within the Community, the host Member State shall provide all the practical support necessary to enable the inspectors to discharge their responsibilities.

Article 39

1. Where the supervisory authorities or the competent authorities of any other Member State are of the opinion that the manufacturer or importer from third countries is no longer fulfilling the obligations laid down in Chapter V of Directive 81/851/EEC they shall forthwith inform the Committee and the Commission, stating their reasons in detail and indicating the course of action proposed.

The same shall apply where a Member State considers that one of the measures envisaged in Chapter VI of Directive 81/851/EEC should be applied in respect of the veterinary medicinal product concerned.

2. The Commission shall in consultation with the Agency forthwith examine the reasons advanced by the Member State concerned. It may request the opinion of the Committee within a time limit to be determined by the Commission having regard to the urgency of the matter. Whenever practicable, the person responsible for marketing shall be invited to provide oral or written explanations.

3. The Commission shall prepare a draft of the Decision to be taken which shall be adopted in accordance with the procedure laid down in Article 31.

However, where a Member State has invoked the provisions of paragraph 4, the time limit provided for in Article 2 c, paragraph 3 of Directive 81/852/EEC shall be reduced to 15 calendar days.

4. In exceptional cases, where action is urgently necessary to protect human or animal health, a Member State may suspend the use on its territory of a veterinary medicinal product which has been authorized in accordance with this Regulation. It shall inform the Commission no later than the following working day of the reasons for its action. The Commission shall immediately consider the reasons given by the Member State in accordance with paragraph 2 and shall initiate the procedure provided for in paragraph 3.

5. A Member State which has adopted the suspensive measures referred to in paragraph 4 may maintain them in force until such time as a definitive Decision has been reached in accordance with the procedure laid down in paragraph 3.

CHAPTER 3

Pharmacovigilance

Article 40

For the purpose of this Chapter, the definitions given in Article 42b of Directive 81/851/EEC shall apply.

Article 41

The Agency, acting in close cooperation with the national pharmacovigilance centres established in accordance with Article 42a of Directive 81/851/EEC, shall be responsible for the collection and evaluation of information about adverse reactions to veterinary medicinal products which have been authorized by the Community in accordance with this Regulation.

The competent authorities of the Member States and the person responsible for marketing shall ensure that all relevant information about adverse reactions to veterinary medicinal products authorized in accordance with this Regulation are brought to the attention of the Agency in accordance with the provisions of this Regulation.

Article 42

The person responsible for marketing a veterinary medicinal product authorized by the Community in accordance with the provisions of this Regulation shall have permanently and continuously at his disposal a person responsible for pharmacovigilance. This person shall be responsible for:

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

b) the preparation and submission of the reports referred to in Article 44 to the competent authorities of the Member States and the Agency in accordance with the requirements of this Regulation;

c) ensuring that any request for the provision of additional information necessary for the evaluation of the benefits and risks of a veterinary medicinal product is answered fully and promptly, including the provision of information about the volume of sales or prescriptions for the veterinary medicinal product concerned, where relevant.

Article 43

1. The person responsible for marketing shall ensure that all suspected serious adverse reactions to a veterinary medicinal product authorized in accordance with the provisions of this Regulation which are brought to his attention by a veterinarian, whether arising within the Community or a third country, are recorded and reported to the Agency within 15 days.

2. In addition, the person responsible for marketing shall be required to maintain detailed records of all other adverse reactions arising within the Community which are reported to him by a veterinarian. Unless other requirements have been laid down as a condition of the granting of authorization by the Community, these records shall be submitted to the Agency immediately upon request or at least every six months during the first two years following authorization and once a year for the following three years. Thereafter, the records shall be submitted at five yearly intervals together with the application for renewal of the authorization, or immediately upon request.

Article 44

Each Member State shall report any suspected serious adverse reaction arising within its territory to a veterinary medicinal product authorized in accordance with this Regulation to the Agency and the person responsible for marketing within 15 days of receipt of a report from a qualified health care professional.

Article 45

The Agency shall, in consultation with Member States, the Commission and interested parties, draw up detailed guidance on the collection, verification and presentation of adverse reaction reports to veterinary medicinal products.

Article 46

1. The Agency shall publish an annual report on the operation of the procedures laid down in this Chapter.

2. Within six years of the entry into force of this Regulation, the Commission shall publish a detailed review of the operation of the procedures laid down in this Chapter and shall propose any amendments which may be necessary to improve the operation of these procedures.

   The Council shall decide on the Commission proposal no later than one year after its submission.

TITLE 4

THE EUROPEAN AGENCY FOR THE EVALUATION OF MEDICINAL PRODUCTS

CHAPTER 1

Tasks of the Agency

Article 47

A European Agency for the Evaluation of Medicinal Products, hereinafter referred to as "the Agency", is hereby established.

Article 48

In order to promote the protection of public health throughout the Community and the adoption of uniform regulatory decisions based on scientific criteria concerning the marketing and use of medicinal products, the objective of the Agency shall be to provide the Member States and the institutions of the Community with the best possible scientific advice on any question relating to the evaluation of the quality, the safety or the efficacy of medicinal products for human or veterinary use which is referred to it in accordance with the provisions of Community legislation relating to medicinal products.

In particular, the Agency shall undertake the following tasks:

a) the coordination of the scientific evaluation of the quality, safety and efficacy of medicinal products which are subject to Community marketing authorization procedures;

b) the presentation of assessment reports, summaries of product characteristics, labels and package inserts for these medicinal products;

c) the continuing supervision, under practical conditions of use, of medicinal products which have been authorized within the Community and the provision of advice on the measures necessary to ensure the safe and effective use of these products, in particular following the evaluation of reports of adverse reactions (pharmacovigilance);

d) coordinating the discharge of the various supervisory responsibilities which have been conferred on the Community and the Member States in particular in respect of the verification of compliance with the principles of good manufacturing practice, good laboratory practice and good clinical practice;

e) to provide technical assistance for the maintenance of a data base on medicinal products which is available for public use;

f) to promote technical cooperation between the Community, its Member States, international organizations and third countries on scientific and technical issues relating to the evaluation of medicinal products;

g) to assist the Community and the Member States in the provision of information about medicinal products to the public;

h) where necessary, to advise and to allow for direct dialogue between the applicant and the Agency on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products.

i) advising on the maximum levels for residues of veterinary medicinal products which may be accepted in foodstuffs of animal origin in accordance with Regulation (EEC) 2377/90.

CHAPTER 2

Structure of the Agency

Article 49

1. The opinion of the Agency on any question relating to the quality, safety or efficacy of medicinal products for human use shall be given by the Committee for Proprietary Medicinal Products.

2. The opinion of the Agency on any question relating to the quality, safety or efficacy of veterinary medicinal products shall be given by the Committee for Veterinary Medicinal Products.

3. In addition to a permanent technical and administrative Secretariat, each Committee may arrange to be assisted by working parties and expert groups.

   The Secretariat shall ensure appropriate coordination between the work of the two Committees.

4. The Committee for Proprietary Medicinal Products and the Committee for Veterinary Medicinal Products may, if they consider it appropriate, seek guidance from the Scientific Council referred to in Article 65 on important questions of a general scientific or ethical nature.

Article 50

1. The Committee for Proprietary Medicinal Products and the Committee for Veterinary Medicinal Products shall each consist of scientific advisors nominated by Member States for a term of three years which shall be renewable. They shall be chosen by reason of their scientific expertise and their role and experience in the evaluation of medicinal products for human and veterinary use as appropriate. Before nominating members to the Committee, the Member States shall consult to ensure that the composition of each Committee reflects the various scientific disciplines necessary for the evaluation of medicinal products.

   The Executive Director or his representative and representatives of the Commission shall be entitled to attend all meetings of the Committees, their working parties and expert groups.

   Members of each Committee may arrange to be accompanied by experts.

2. In addition to their task of providing an objective scientific advice to the Community and Member States on the questions which are referred to them, the members of each Committee shall ensure that there is appropriate coordination between the work of the Agency and the work of scientific advisory bodies established in Member States.

3. The Member States shall refrain from giving any instruction to Members of the Committtees which is incompatible with the tasks referred to in paragraph 2.

Article 51

1. The Member States shall transmit to the Executive Director a list of rapporteurs and experts with proven experience in the evaluation of the quality, safety and efficacy of medicinal products, together with an indication of their qualifications and specific areas of expertise.

   This list shall be updated as necessary.

2. On a proposal from the Committee for Proprietary Medicinal Products or the Committee for Veterinary Medicinal Products, the Executive Director may entrust specific tasks to rapporteurs or experts. The Provision of services by rapporteurs or experts shall be governed by a written contract between the Agency and the person concerned, or where appropriate between the Agency and his employer. The person concerned, or his employer, shall be remunerated in accordance with a fixed scale of fees to be established by the financial regulation adopted by the Management Board.

3. The Executive Director may also have recourse to the services of experts for the discharge of other specific responsibilities of the Agency, in particular the inspections referred to in Articles 8, 17, 29 and 38.

Article 52

1. The Membership of the Committee for Proprietary Medicinal Products and the Committee for Veterinary Medicinal Products shall be made public. When each appointment is published, the professional qualifications of each member shall be specified.

2. Committee members, rapporteurs or experts may not hold financial or other interests in the pharmaceutical industry which could affect their impartiality. All indirect interests which could relate to this industry shall be entered in a register held by the Executive Director which the public may consult.

Article 53

1. The Executive Director shall be appointed by the management board, on a proposal from the Commission, for a period of five years, which shall be renewable.

2. The Executive Director shall be the legal representative of the Agency. He shall be responsible:
   - for the day to day administration of the Agency;
   - for the provision of appropriate scientific and technical support for the Committee for Proprietary Medicinal Products and the Committee for Veterinary Medicinal Products, and their working parties and expert groups;
   - for ensuring that the time limits laid down in Community legislation for the adoption of Opinions by the Agency are respected;
   - for ensuring appropriate coordination between the Committee for Proprietary Medicinal Products and the Committee for Veterinary Medicinal Products;
   - for the preparation of the statement of revenue and expenditure and the execution of the budget of the Agency;
   - for all staff matters.

3. Each year, the Executive Director shall submit to the Management Board for approval:
   - a draft report covering the activities of the Agency in the previous year, including information about the number of applications evaluated within the Agency, and the time taken for the completion of the evaluation;
   - a draft programme of work for the coming year;
   - the draft annual accounts for the previous year;
   - the draft budget for the coming year.

4. The Executive Director shall approve all financial expenditure of the Agency.

Article 54

1. The Management Board shall consist of two representatives from each Member State and two representatives of the Commission. One representative shall have specific responsibilities relating to medicinal products for human use and one relating to veterinary medicinal products.

2. The term of office of the representatives shall be three years. It shall be renewable.

3. The Management Board shall elect its Chairman for a term of three years and shall adopt its rules of procedure.

   Decisions of the management board shall be adopted by a two-thirds majority.

4. The Executive Director shall provide the Secretariat of the Management Board and shall be entitled to attend the meetings of the Board unless it decides otherwise. In this case, a representative of the Commission shall prepare the record of the meeting.

5. Before 31 January each year, the Management Board shall adopt the general report on the activities of the Agency for the previous year and its programme of work for the coming year and forward them to the Member States, the Commission, the Council, the European Parliament and the Scientific Council.

CHAPTER 3

Financial Provisions

Article 55

1. The revenues of the Agency shall consist of a contribution from the Community, and the fees paid by undertakings for obtaining a Community marketing authorization and for other services provided by the Agency.

2. The expenditure of the Agency shall include the staff, administrative, infrastructure and operational expenses and expenses resulting from contracts entered into with third parties.

3. Before 31 January each year the Management Board shall draw up an estimate of revenue and expenditure which shall be in balance for each financial year which shall be the same as a calendar year. This estimate shall be forwarded to the Commission and the Member States.

4. The Commission shall include an appropriate contribution to the Agency in the preliminary draft budget of the European Communities. The budget of the European Communities shall each year under a specific heading in the operational part include a contribution to the Agency.

5. The Management Board, after obtaining the opinion of the Commission, shall adopt the statement of revenue and expenditure at the beginning of the financial year adjusting it to the contribution granted to the Agency and to its other resources.

6. The Management Board shall adopt the financial regulations of the Agency, in agreement with the Commission.

7. Before 31 March each year, the Management Board shall transmit to the Commission and to the Court of Auditors the accounts for all revenues and expenditure by the Agency during the preceding year. The Court of Auditors shall examine the accounts in accordance with the provisions of Article 206a of the EEC Treaty.

8. Before 31 October each year, the Commission shall submit the accounts and the report of the Court of Auditors to the Council together with its own observations. The Management Board shall be discharged in respect of the implementation of the budget in accordance with the procedure laid down in Article 206b of the EEC Treaty.

Article 56

The fees referred to in Article 55, paragraph 1, shall be established by the Council on a proposal from the Commission, following consultation of organizations representing the interests of the pharmaceutical industry at the Community level.

CHAPTER 4

General Provisions governing the Agency

Article 57

The Agency shall have legal personality. In all Member States it shall benefit from the widest powers granted by law to legal persons. In particular it may acquire and dispose of real property and chattels and institute legal proceedings.

Article 58

1. The contractual liability of the Agency shall be governed by the law applicable to the contract in question. The Court of Justice of the European Communities shall have jurisdiction to give judgement pursuant to any arbitration clause contained in a contract concluded by the Agency.

2. In the case of non-contractual liability, the Agency shall, in accordance with the general principles common to the laws of the Member States, make good any damage caused by itself or by its servants in the performance of their duties.

   The Court of Justice shall have jurisdiction in any dispute relating to compensation for such damages.

3. The personal liability of its servants towards the Agency shall be governed by the relevant conditions applying to the staff of the Agency.

Article 59

Member States, members of the Management Board and third parties directly involved may refer to the Commission any act of the Agency, whether express or implied, for the Commission to examine the legality of that Act.

Referral to the Commission shall be made within 15 days of the day on which the party concerned first became aware of the act in question.

The Commission shall take a Decision within one month. If no Decision has been taken within this period, the case shall be deemed to have been dismissed.

Article 60

The Protocol on the Privileges and Immunities of the European Communities shall apply to the Agency.

Article 61

1. Apart from officials and other staff seconded by an institution of the European Communities, the Agency shall have its own personnel to whom will be applied a special regime, to be decided by a Council Regulation, adopted by a qualified majority on a proposal from the Commission.

2. In respect of its personnel, the Agency shall exercise the powers which have been devolved to the Authority invested with the power of nomination.

3. The Management Board, in agreement with the Commission, shall adopt the necessary implementing provisions.

Article 62

Members of the Management Board, the Executive Director, the staff of the Agency, the members of Committees attached to the Agency and their working parties, experts and any other persons participating in the work of the Agency, including observers, shall be obliged, even after their duties have ceased, not to disclose information of the kind covered by the obligation of professional secrecy.

Article 63

The Management Board may, in agreement with the Commission, invite representatives of international organizations with interest in the scientific and technical evaluation of medicinal products such as:

- the European Pharmacopoeia,
- the European Free Trade Association,
- the Nordic Council on Medicines,
- the World Health Organization,

to participate as observers in the work of the Agency.

Article 64

The Management Board shall, in agreement with the Commission, develop appropriate contacts between the Agency and the representatives of the industry, consumers and patients and the professions.

Article 65

1. A Scientific Council shall be established and attached to the Agency.

2. The Scientific Council shall consist of not less than 5 and not more than 9 persons of outstanding and internationally recognised ability with particular knowledge of scientific and ethical issues relating to medicinal products for human or veterinary use.

3. The Members of the Scientific Council shall be nominated by the Council on a proposal from the Commission for a term of 4 years. Their appointments shall be renewable.

4. The Scientific Council shall advise for the Committee for Proprietary Medicinal Products or the Committee for Veterinary Medicinal Products on any question which is submitted to it in accordance with Article 49. In addition, the Scientific Council shall be able to comment on the annual report on the operation of the Agency prepared in accordance with Article 55.

Article 66

The Agency shall take up its responsibilities on 1 January 1993.

TITLE 5

GENERAL AND FINAL PROVISIONS

Article 67

All Decisions to grant, refuse, amend, suspend, withdraw or revoke a marketing authorization which are taken in accordance with this Regulation shall state in detail the reasons on which they are based. Such Decisions shall be notified to the party concerned, who shall be able to exercise the remedies conferred upon him under the EEC Treaty.

Article 68

1. An authorization to market a medicinal product coming within the scope of this Regulation shall not be refused, amended, suspended, withdrawn or revoked except on the grounds set out in this Regulation.

2. An authorization to market a medicinal product coming within the scope of this Regulation shall not be granted, refused, amended, suspended, withdrawn or revoked except in accordance with the procedures set out in this Regulation.

Article 69

In respect of medicinal products coming within the scope of this Regulation, and in order to exercise the responsibilities imposed upon them by this Regulation, the competent authorities of the Community shall be able to exercise all the powers conferred on the competent authorities of the Member States by Directives 65/65/EEC, 75/319/EEC, and 81/851/EEC.

Article 70

Without prejudice to Article 68, and without prejudice to the Protocol on the Privileges and Immunities of the European Communities, each Member State shall determine the penalties to be applied for the infringement of the provisions of this Regulation. The penalties shall be sufficient to promote compliance with those measures.

Member States shall forthwith inform the Commission of the institution of any infringement proceedings.

Article 71

Within three years of the entry into force of this Regulation the Commission shall produce a report on whether the level of harmonization achieved by the present Regulation and by Council Directive 90/167/CEE of 26 March 1990 laying down the conditions governing the preparation, placing on the market and use of medicated feedingstuffs[16] is equivalent to that provided for in Council Directive 70/524/EEC of 23 November 1970 concerning additives in animal feedingstuffs[17], accompanied if necessary by the proposals to modify the status of the coccidiostats and other medicinal substances covered by that Directive.

The Council shall decide on the Commission proposals no later than one year after their submission.

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(16) OJ No L 92, 7.4.90, p. 42.

(17) OJ No L 270, 14.12.70, p. 1.

Article 72

Within six years of the entry into force of this Regulation, the Commission shall publish a general report on the experience acquired as a result of the operation of the procedures laid down in this Regulation, in Chapter III of Directive 75/319/EEC and in Chapter IV of Directive 81/851/EEC together with any appropriate proposals for amendments to Article 3 and the Annex in order to extend the scope of the procedures laid down in this Regulation to other categories of medicinal products, on an obligatory or a voluntary basis.

The Council shall decide on the Commission proposals no later than one year after their submission.

Article 73

This Regulation shall enter into force on the third day following its publication in the Official Journal of the European Communities.

Titles 1,2, 3 and 5 shall apply from 1 January 1993.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels

For the Council

ANNEX

PART A

Medicinal products developed by means of one of the following biotechnological processes:

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

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.

PART B

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 use in human beings;

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.

Proposal for a

COUNCIL DIRECTIVE (EEC)

amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC
in respect of medicinal products

Proposal for a

COUNCIL DIRECTIVE (EEC)

amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC
in respect of medicinal products

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community, and in particular Article 100a thereof;

Having regard to the proposal from the Commission(1),

In cooperation with the European Parliament(2),

Having regard to the opinion of the Economic and Social Committee(3),

Whereas it is important to adopt measures with the aim of progressively establishing the internal market over a period expiring on 31 December 1992; whereas the internal market shall comprise an area without internal frontiers in which the free movement of goods, persons, services and capital is ensured;

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(1)

(2)

(3)

Whereas Article 15(2) of Second Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products[4] as last amended by Directive 89/381/EEC[5], provides that the Commission shall submit to the Council a proposal containing appropriate measures leading towards the abolition of any remaining barriers to the free movement of proprietary medicinal products;

Whereas in the interests of public health it is necessary that decision on the authorization to place medicinal products on the market be exclusively based on the criteria of quality, safety and efficacy; whereas these criteria have been extensively harmonized by Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products[6], as last amended by Directive 89/381/EEC, and by Directive 75/319/EEC, and by Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of the Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of medicinal products[7] as last amended by Directive 89/341/EEC[8]; whereas, however Member States should exceptionally be able to prohibit the use on their territory of medicinal products which infringe objectively defined concepts of public order or public morality;

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(4) OJ No L 147, 9.6.1975, p. 13.

(5) OJ No L 181, 28.6.1989, p. 44.

(6) OJ No 22, 9.2.65, p. 369/65.

(7) OJ No L 147, 9.6.75, p. 1.

(8) OJ No L 142, 25.5.1989, p. 11.

Whereas, with the exception of those medicinal products which are subject to the centralized Community authorization procedure established by Council Regulation (EEC) ..../.., of ../.../.. laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products[9], an authorization to place a medicinal product on the market in one Member State ought in principle to be recognized by the competent authorities of the other Member States unless there are serious grounds for supposing that the authorization of the medicinal product concerned may present a risk to public health; whereas, in the event of a disagreement between Member States about the quality, the safety or the efficacy of a medicinal product, a scientific evaluation of the matter should be undertaken by the Committee for Proprietary Medicinal Products 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; whereas this Decision should be adopted by a rapid procedure ensuring close cooperation between the Commission and the Member States, in particular through the Standing Committee on Medicinal Products for Human Use created by Article 2b of Directive 75/318/EEC;

Whereas in order better to protect public health and avoid any unnecessary duplication of effort during the examination of application for authorization to place medicinal products on the market, Member States should systematically prepare assessment reports in respect of each medicinal product which is authorized by them, and exchange the reports upon request; whereas, furthermore, a Member State should be able to suspend the examination of an application for authorization to place a medicinal product on the market which is currently under active consideration in another Member State with a view to recognizing the Decision reached by the latter Member State;

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(9)

Whereas following the establishment of the internal market, specific controls to guarantee the quality of medicinal products imported from third countries can only be waived if appropriate arrangements have been made by the Community to ensure that the necessary controls are carried out in the exporting country;

Whereas it is desirable to codify and improve the cooperation and exchange of information between Member States relating to the supervision of medicinal products and in particular the monitoring of adverse reactions under practical conditions of use through the national pharmacovigilance centres,

HAS ADOPTED THIS DIRECTIVE:

Article 1

Directive 65/65/EEC is hereby amended as follows:

1. Article 3 is replaced by the following:

"Article 3

No medicinal product may be placed on the market of a Member State unless an authorization has been issued by the competent authority of that Member State or by the Community.

2. In the second paragraph of Article 4, points 6 and 11 are are replaced by the following :

"6. Posology, pharmaceutical form, method and route of administration and expected shelf life.

If applicable, reasons for any precautionary and safety measures to be taken for the storage of the product, its administration to patients and for the disposal of waste products, together with an indication of any potential risks presented by the product for the environment."

"11. Copy of any authorization obtained in another Member State or in a third country to place the relevant medicinal product on the market, together with a list of those Member States in which an application for authorization submitted in accordance with this Directive is under examination and copies of the summary of product characteristics proposed by the applicant in accordance with Article 4a or approved by the comptetent authorities in accordance with Article 4b, as appropriate, in respect of each Member State concerned. Details of any Decision to refuse authorization, whether in the Community or a third country and the reasons for that Decision.

This information shall be updated at regular intervals."

3. Article 4b is replaced by the following:

"Article 4b

When the marketing authorization referred to in Article 3 is issued, the person responsible for placing that product on the market shall be informed, by the competent authorities of the Member State concerned, of the summary of the product characteristics as approved by them. The competent authorities shall take all necessary measures to ensure that the information given in the summary is in conformity with that accepted when the marketing authorization is issued or subsequently. The competent aurthorities shall forthwith forward a copy of the summary to the European Agency for the Evaluation of Medicinal Products established by Council Regulation (EEC) ..../..(*)

Furthermore, the competent authorities shall draw up an assessment report and comments on the dossier as regards the results of the analytical, pharmaco-toxicological tests and the clinical trials of the medicinal product concerned. The assessment report shall be updated whenever new information becomes available which is of importance for the evaluation of the quality, safety or efficacy of the medicinal product concerned.

(*) OJ No L "

4. Article 6 is replaced by the following:

"Article 6

This Directive shall not affect the application of national legislation prohibiting or restricting the use of medicinal products as contraceptives or abortifacients. The Member States shall communicate the national legislation concerned to the Commission."

5. Article 7 is replaced by the following:

"Article 7

1. Member States shall take all appropriate measures to ensure that the procedure for granting an authorization to place a medicinal product on the market is completed within 210 days of the date of submitting the application.

2. Where a Member State notes that an application for authorization submitted after 1 January 1993 is already under active examination in another Member State, the former Member State may decide to suspend the detailed examination of the application in order to await the assessment report prepared by the first Member State in accordance with Article 4b."

The Member State concerned shall inform the first Member State and the applicant 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 first Member State shall forward a copy of its assessment report to the Member State concerned.

Within 90 days of the receipt of the assessment report, the Member State concerned shall recognise the Decision of the first Member State. However, if the Member State concerned considers that there are serious grounds for supposing that the authorization of the medicinal product may present a risk to public health, it shall inform the first Member State, the Committee for Proprietary Medicinal Products and the applicant within the time limit referred to above, stating its reasons in detail, and apply the procedures laid down in Chapter III of Directive 75/319/EEC."

6. The following Article 7a is inserted:

"Article 7a

1. With effect from 1 January 1996, where a Member State is informed in accordance with point 11 of the second paragraph of Article 4 that another Member State has authorized a medicinal product which is the subject of an application for authorization in the Member State concerned, that Member State shall forthwith request the authorities of the Member State which has granted the authorization of the Member State which has granted the authorization to forward to it the assessment report referred to in the second paragraph of Article 4b. Within 90 days of the receipt of the assessment report, the competent authorities of the Member State concerned shall recognise the authorization granted by the other Member State.

2. Notwithstanding paragraph 1, if the Member State concerned considers that there are serious grounds for supposing that the authorization of the medicinal product may present a risk to public health, it shall inform the Member State which granted the initial authorization, any other Member States concerned by the application, and the Committee for Proprietary Medicinal Products and the applicant within the time limit referred to in paragraph 1, stating its reasons in detail, and apply the procedures laid down in Chapter III of Directive 75/319/EEC."

7. Article 9a is replaced by the following:

"Article 9a

After an authorization has been issued, the person responsible for placing the product on the market must, in respect of the methods of production and control provided for in points 4 and 7 of the second paragraph of Article 4, take account of technical and scientific progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods. These changes must be accepted by the comptetent authorities of the Member State concerned.

8. Article 10 is replaced by the following:

"Article 10

1. Authorization shall be valid for five years and shall be renewable for five year periods, on application by the holder at least three months before the expiry date.

2. In exceptional circumstances, and following consultation with the applicant, an authorization may be granted subject to such conditions as appear necessary to ensure the protection of public health, including specific obligations to conduct further studies following the granting of authorization and specific obligations in respect of the reporting of adverse reactions to the medicinal product."

Article 2

In Directive 75/318/EEC, the Committee referred to in Article 2b is hereby renamed "the Standing Committee on Medicinal Products for Human Use".

Article 3

Directive 75/319/EEC is hereby amended as follows :

1. Chapter III is replaced by the following:

"CHAPTER III

Committee for Proprietary Medicinal Products

Article 8

1. In order to facilitate the adoption of common Decisions by Member States on the authorization of medicinal products for human use on the basis of the scientific criteria of quality, safety and efficacy, and to achieve thereby the free movement of medicinal products, within the Community, a Committee for Proprietary Medicinal Products, hereinafter referred to as "the Committee", is hereby set up. The Committee shall be attached to the European Agency for the Evaluation of Medicinal Products established by Council Regulation (EEC) ..../..,(*) hereinafter referred to as the Agency.

2. In addition to the other responsibilities conferred upon it by Community law, the Committee shall examine any question relating to the grant, amendment, suspension or withdrawal of authorization for a medicinal product which is submitted to it in accordance with the provisions of this Directive.

3. The Committee shall adopt its own rules of procedure.

Article 9

1. In order to obtain the recognition in one or more of the Member States of an authorization issued by a Member State in accordance with Article 3 of Directive 65/65/EEC, the holder of the authorization shall submit an application to the competent authorities of the Member State or Member States concerned, together with the information and particulars referred to in Articles 4, 4a and 4b of Directive 65/65/EEC. He shall testify to the identity of the dossier with that accepted by the first Member State, or shall identify any additions or modifications it may contain. In the latter case, he shall certify that the summary of product characteristics proposed by him in accordance with Article 4a of Directive 65/65/EEC is identical to that accepted by the first Member State in accordance with Article 4b of Directive 65/65/EEC. Moreover, he shall certify that all the dossiers filed as part of this procedure are identical.

2. The holder of the marketing authorization shall notify the Committee of this application, inform it of the Member States concerned and of the dates of submission of the application and send it a copy of the authorization granted by the first Member State. He shall also send the Committee copies of any marketing authorization which may have been granted by the other Member States in respect of the product concerned, and shall indicate whether any application for authorization is currently under consideration in any Member State.

3. The holder of the authorization shall also inform the Member State which granted the initial authorization that an application is being made in accordance with this Directive and shall notify it of any additions to the original dossier; that Member State may require the applicant to provide it with all the particulars and documents necessary to enable it to check the identity of the dossiers filed with the dossier on which it took its Decision. In addition that Member State shall forward to the Member State or Member States concerned by the application a copy of the assessment report established in accordance with the second paragraph of Article 4b of Directive 65/65/EEC.

4. Each Member State concerned shall recognise the marketing authorization granted by the first Member State within 90 days of receipt of the application. It shall inform the Member State which granted the initial authorization, the other Member States concerned by the application, the Committee, and the person responsible for marketing thereof.

Article 10

1. Notwithstanding Article 9(4), where a Member State considers that there are serious grounds for supposing that the authorization of the medicinal product concerned may present a risk to public health, it shall forthwith inform the applicant, the Member State which granted the initial authorization, any other Member States concerned by the application and the Committee. The Member State shall state its reasons in detail and shall indicate what action may be necessary to correct any defect in the application.

2. All the Member States concerned shall use their best endeavours to reach agreement on the action to be taken in respect of the application. They shall provide the applicant with the possibility to make his point of view known orally or in writing. However, if within 60 days of the expiry of the time limit referred to in Article 9 (4), the Member States have not been able to reach agreement they shall forthwith refer the matter to the Committee for the application of the procedure laid down in Article 13.

3. Within the time limit referred to in paragraph 2, the Member States concerned 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. A copy of this information shall be provided to the applicant.

4. As soon as he is informed that the matter has been referred to the Committee, the applicant shall forthwith forward to the Committee a copy of the information and particulars referred to in Article 9 (1).

Article 11

If several applications submitted in accordance with Articles 4 and 4a of Directive 65/65/EEC have been made for marketing authorization for a particular medicinal product, and Member States have adopted divergent Decisions concerning the authorization of the medicinal product, or its suspension or withdrawal from the market, any Member State, or the Commission, or the person responsible for marketing may refer the matter to the Committee for application of the procedure laid down in Article 13.

The Member State concerned, the person responsible for marketing or the Commission shall clearly identify the question which is referred to the Committee for consideration and, if necessary, shall inform the person responsible for marketing.

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

Article 12

The Member States or the Commission 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 13 before reaching a Decision on a request for a marketing authorization or on the suspension or revocation of an authorization, or on any other amendment to the terms of a marketing authorization which appears necessary, in particular to take account of the information collected in accordance with Chapter Va of this Directive.

The Member State concerned or the Commission shall clearly identify the question which is referred to the Committee for consideration and shall inform the person responsible for marketing.

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

Article 13

1. 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.

   In case of urgency, on a proposal from its Chairman, the Committee may agree to impose a shorter deadline.

2. In order to consider the matter, the Committee may appoint one of its Members to act as rapporteur. The Committee may also appoint individual experts to advise it on specific questions. When appointing experts, the Committee shall define their tasks and specify the time limit for the completion of these tasks.

3. In the cases referred to in Article 10 and 11, before issuing its opinion, the Committee shall provide the person responsible for marketing with an opportunity to present written or oral explanations.

   In the case referred to in Article 12, the person responsible for placing the medicinal product on the market may be asked to explain himself orally or in writing.

   If it considers it appropriate, the Committee may invite any other person to provide information relating to the matter before it.

   The Committee may suspend the time limit referred to in paragraph 1 in order to allow the person responsible for marketing to prepare explanations.

4. Where the opinion of the Committee is that :

   - the application does not satisfy the criteria for authorization set out in this Directive, or
   - the summary of product characteristics proposed by the applicant in accordance with Article 4a of Directive 65/65/EEC should be amended, or
   - the labelling or package leaflet of the product is not in compliance with Direcive ../.../EEC, or
   - the authorization should granted subject to conditions, or
   - an existing marketing authorization should be suspended amended or withdrawn;

   the Agency shall forthwith inform the person responsible for marketing. Within 15 days of the receipt of the opinion, the person responsible for marketing may provide written notice to the Agency that he wishes to appeal. Within 60 days of the receipt of the grounds for appeal, the Committee shall consider whether its opinion should be revised, and the reasons for the conclusions reached on the appeal shall be annexed to the assessment report referred to in paragraph 5.

5. Within 30 days of its adoption, the Agency shall forward the final opinion of the Committee to the Commission, the Member States and the person responsible for marketing together with a report, describing the assessment of the medicinal product and the reasons for its conclusions.

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

   a) a draft summary of the product characteristics, as referred to in Article 4a of Directive 65/65/EEC;

b) details of any conditions or restrictions which should be imposed on the supply or use of the medicinal product concerned, included the conditions under which the medicinal product may be made available to patients, having regard to the criteria laid down in Directive ../.../EEC concerning the legal status for the supply of medicinal products for human use;

c) the draft text of the labelling and package leaflet, proposed by the applicant presented in accordance with Directive ../.../.. on the labelling of medicinal products for human use and on package leaflets.

Article 14

1. Within 30 days of the receipt of the opinion of the Committee, the Commission shall prepare a draft of the Decision to be taken in respect of the application taking into account the objectives of Community policies and considering all relevant information. In the event of a draft Decision which envisages the granting of a marketing authorization, the documents referred to in points (a), (b) and (c) of Article 13(5) shall be annexed. The Commission shall transmit the draft Decision to the Member States and to the applicant.

   The Commission shall explain in detail the reasons for any differences between the draft Decision and the opinion of the Committee.

2. The Commission shall adopt the Decision to be taken in respect of the application unless, within 30 days, it has received a reasoned request from a Member State to reconsider the matter. The Member State concerned shall also transmit a copy of its request to the other Member States and the applicant within the same time limit.

3. Within the time limit referred to in paragraph 2, the applicant may submit written observations on the draft Decision for consideration by the Commission.

4. The Commission shall examine any reasoned request received in accordance with paragraph 2, in consultation with the Agency, and after consideration of any further observations submitted by the applicant.

If the Commission considers that the request raises questions of a scientific or technical nature requiring further examination, it may remit the matter to the Agency. In this case the Committee shall give a second opinion within a time limit of 60 days. Within 30 days of the receipt of the opinion, the Commission shall adopt the Decision to be taken in respect of the application.

Otherwise the Decision shall be taken in accordance with the procedure laid down in Article 2b and 2c of Directive 75/318/EEC.

5. A Decision adopted in accordance with this Article shall be addressed to the Member States concerned by the matter and to the person responsible for marketing. The Member States shall either grant or withdraw marketing authorization, or make any adjustment to the terms of a marketing authorization which may be necessary to comply with the Decision within 30 days of its notification. They shall inform the Commission and the Committee thereof.

Article 15

Any application by the person responsible for marketing to amend the terms of a marketing authorization which has granted in accordance with the provisions of this Chapter shall be submitted to all the Member States which have previously authorized the medicinal product concerned.

The Agency shall, in consultation with the Commission, adopt appropriate arrangements for the examination by the Committee of amendments or variations to a marketing authorization which has been granted in accordance with the provisions of this Chapter.

The procedures laid down in Articles 13 and 14 shall apply by analogy to variations and amendments of marketing authorizations.

Article 15a

1. Where a Member State considers that the amendment of the terms of a marketing authorization which has been granted in accordance with the provisions of this Chapter or its suspension or withdrawal is necessary, the Member State concerned shall forthwith refer the matter to the Committee for the application of the procedures laid down in Articles 13 and 14.

2. In exceptional cases, where action is urgently necessary to protect public health, until a definitive decision is adopted, a Member State may suspend the use of the medicinal product concerned on its territory. It shall inform the Commission no later than the following working day of the reasons for its action.

Article 15b

Articles 15 and 15a shall apply by analogy to medicinal products authorized by Member States following an opinion of the Committee given in accordance with Article 4 of Directive 87/22/EEC before 1 January 1993.

Article 15c

1. The Agency shall publish an annual report on the operation of the procedures laid down in this Chapter.

2. Within six years of the date referred to in the first sub-paragraph of Article 4 (1), the Commission shall publish a detailed review of the operation of the procedures laid down in this chapter and shall propose any amendments which may be necessary to improve the operation of these procedures.

   The Council shall decide on the Commission proposal within one year of its submission.

(*) OJ No L "

2. The third sub-paragraph of paragraph 1 of Article 22 is replaced by the following:

"In the case of medicinal products imported from a third country, where appropriate arrangements have been made by the Community with the exporting country to ensure that the manufacturer of the medicinal product applies standards of good manufacturing practice at least equivalent to those laid down by the Community and to ensure that the controls referred to under (b) have been carried out in the exporting country, the qualified person may be relieved of responsibility for those controls."

3. The following Chapter Va is inserted after Article 29:

"CHAPTER Va

Pharmacovigilance

Article 29a

In order to ensure the adoption of appropriate regulatory decisions concerning the continued authorization of medicinal products within the Community, having regard to information obtained about adverse reactions to medicinal products under practical conditions of use, the Member States shall establish a pharmacovigilance system for collecting information about adverse reactions to medicinal products in human beings and for the scientific evaluation of such information.

Article 29b

For the purpose of this Directive, the following definitions shall apply:

- "adverse reaction" shall mean a reaction which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the modification of physiological function.

- "serious adverse reaction" shall mean an adverse reaction which is fatal, life-threatening, disabling, incapacitating, or which results in hospitalisation or prolonged hospitalisation.

Article 29c

The person responsible for marketing shall have permanently and continuously at his disposal a person responsible for pharmacovigilance. This person shall be responsible for :

a) the establishment and maintenance of a system which ensures that information about all adverse reactions which are reported to the personnel of the company, including its sales personnel and medical representatives, is collected and collated at a single point;

b) the preparation and submission to the competent authorities of the reports referred to in Article 29d, in such form as may be laid down by those authorities.

c) ensuring that any request from the competent authority for the provision of additional information necessary for the evaluation of the benefits and risks of a medicinal product is answered fully and promptly, including the provision of information about the volume of sales or prescriptions for the medicinal product concerned, where relevant.

Article 29d

1. The person responsible for marketing shall be required to record and to report all suspected serious adverse reactions which are brought to his attention by a qualified health care professional to the competent authorities within 15 days of their receipt.

2. In addition, the person responsible for marketing shall be required to maintain detailed records of all other adverse reactions which are reported to him by a qualified health care professional. Unless other requirements have been laid down as a condition of the granting of authorization, these records shall be submitted to the competent authorities immediately upon request or at least every six months during the first two years following authorization, and once a year for the following three years. Thereafter, the records shall be submitted at five yearly intervals together with the application for renewal of the authorization, or immediately upon request.

Article 29e

The Member States shall take all appropriate measures to encourage doctors and other health care professionals to report adverse reactions to the competent authority.

The Member States may impose specific requirements on medical practitioners, in particular in respect of the reporting of serious or unexpected adverse reactions, or where such reporting is a condition of the marketing authorization.

Article 29f

The Member States shall ensure that reports of serious adverse reactions are brought to the attention of the Agency and the person responsible for marketing within 15 days of their receipt.

Article 29g

In order to facilitate the exchange of information about pharmacovigilance within the Community, the Agency shall, in consultation with Member States, the Commission and interested parties, draw up detailed guidance on the collection, verification and presentation of adverse reaction reports.

Article 29h

Where as a result of the evaluation of adverse reaction reports, a Member State is considering amending the terms of a marketing authorization or its suspensions or withdrawal, it shall forthwith inform the Agency.

In case of urgency, the Member State concerned may suspend the marketing of a medicinal product, provided the Agency is informed at the latest on the following working day."

Article 4

Member States shall take all appropriate measures to comply with the provisions of this Directive, with the exception of Article 1 (6), before 1 January 1993. They shall forthwith inform the Commission thereof.

Member States shall take all appropriate measures to comply with Article 1 (6) of this Directive before 1 January 1996. They shall forthwith inform the Commission thereof.

When Member States adopt these provisions, these shall contain a reference to this Directive or shall be accompanied by such reference at the time of their official publication. The procedure for such reference shall be adopted by Member States.

Article 5

This Directive is addressed to the Member States.

Done at Brussels

For the Council

Proposal for a

COUNCIL DIRECTIVE

amending Directives 81/851/EEC and 81/852/EEC
In respect of veterinary medicinal products

Proposal for a

COUNCIL DIRECTIVE

amending Directives 81/851/EEC and 81/852/EEC
in respect of veterinary medicinal products

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community, and in particular Article 100a thereof;

Having regard to the proposal from the Commission(1),

In cooperation with the European Parliament(2),

Having regard to the opinion of the Economic and Social Committee(3),

Whereas it is important to adopt measures with the aim of progressively establishing the internal market over a period expiring on 31 December 1992; whereas the internal market shall comprise an area without internal frontiers in which the free movement of goods, persons, services and capital is ensured;

Whereas despite the progress achieved by Directive 81/851/EEC of 28 September 1981 on the approximation of the laws of the Member States relating to veterinary medicinal products(4), as last amended by Directive ../.../EEC of .....(5), further measures are necessary to abolish the remaining barriers to the free movement of veterinary medicinal products within the Community;

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(1)
(2)
(3)
(4) OJ No L 317, 6.11.1981, p. 1.
(5)

Whereas, with the exception of those veterinary medicinal products which are subject to the centralized Community authorization procedure established by Council Regulation (EEC) ..../.., of ../.../.. laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products[6], an authorization to place a veterinary medicinal product on the market in one Member State ought in principle to be recognized by the competent authorities of the other Member States unless there are serious grounds for supposing that the authorization of the veterinary medicinal product concerned may present a risk to human or animal health, or to the environment; whereas, 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 Committee for Veterinary Medicinal Products 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; whereas this Decision should be adopted by a rapid procedure ensuring close cooperation between the Commission and the Member States, in particular through the Standing Committee on Veterinary Medicinal Products created by Article 2b of Council Directive 81/852/EEC of 28 September 1981 on the approximation of the laws of Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of veterinary medicinal products[7], as last amended by Directive 87/20/EEC[8];

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(6)
(7) OJ No L 317, 6.11.81, p. 16.
(8) OJ No L 15, 17.1.87, p. 34.

Whereas in order better to protect human an animal health and avoid any unnecessary duplication of effort during the examination of applications for authorization to place veterinary medicinal products on the market, Member States should systematically prepare assessment reports in respect of each veterinary medicinal product which is authorized by them, and exchange the reports upon request; whereas, furthermore, a Member State should be able to suspend the examination of an application for authorization to place a veterinary medicinal product on the market which is currently under active consideration in another Member State with a view to recognizing the Decision reached by the latter Member State;

Whereas following the establishment of the internal market, specific controls to guarantee the quality of veterinary medicinal products imported from third countries can only be waived if appropriate arrangements have been made by the Community to ensure that the necessary controls are carried out in the exporting country;

Whereas it is desirable to codify and improve the cooperation and exchange of information between Member States relating to the supervision of veterinary medicinal products and in particular the monitoring of adverse reactions under practical conditions of use through the national pharmacovigilance centres;

Whereas in order to improve the protection of public health it is necessary to specify that foodstuffs for human consumption may not be taken from animals which have been used in clinical trials of veterinary medicinal products unless a provisional maximum residue level has been laid down for residues of the veterinary medicinal product concerned in accordance with the provisions of Council Regulation (EEC) 2377/90 laying down a Community procedure for the establishment of maximum residue levels for residues of veterinary medicinal products(9),

HAS ADOPTED THIS DIRECTIVE :

(9) OJ No L 224, 18.8.1990, p. 1.

Article 1

Directive 81/851/EEC is hereby amended as follows :

1. In Article 4, the first sub-paragraph of paragraph 1 is replaced by the following :

"No veterinary medicinal product may be placed on the market of a Member State unless an authorization has been issued by the competent authority of that Member State or by the Community."

2. In Article 4, the following sub-paragraph is inserted at the end of paragraph 2.

"The Member States shall not permit foodstuffs for human consumption to be taken from test animals unless a provisional maximum residue level has been established by the Community in accordance with the provisions of Regulation (EEC) 2377/90 (*) and an appropriate withdrawal period has been established to ensure that this level will not be exceeded in the foodstuffs.

(*) OJ No L 224, 18.8.1990, p. 1."

3. In the second paragraph of Article 5, point 13 is replaced by the following :

13. Copy of any authorization obtained in another Member State or in a third country to place the relevant veterinary medicinal product on the market, together with a list of those Member States in which an application for authorization submitted in accordance with this Directive is under examination and copies of the summary of product characteristics proposed by the applicant in accordance with Article 5a or approved by the competent authorities in accordance with Article 5b, as appropriate, in respect of each Member State concerned. Details of any Decision to refuse authorization, whether in the Community or a third country and the reasons for that Decision.

This information shall be updated at regular intervals."

4. Article 5b is replaced by the following :

"Article 5b

When the marketing authorization referred to in Article 4 (1) is issued, the person responsible for placing that product on the market shall be informed, by the competent authorities of the Member state concerned, of the summary of the product characteristics as approved by them. The competent authorities shall take all necessary measures to ensure that the information given in the summary is in conformity with that accepted when the marketing authorization is issued or subsequently. The competent authorities shall forthwith forward a copy of the summary to the European Agency for the Evaluation of Medicinal Products established by Council Regulation (EEC..../....(*)

Furthermore, the competent authorities shall draw up an assessment report and comments on the dossier as regards the results of the analytical, pharmaco-toxicological tests and the clinical trials of the veterinary medicinal product concerned. The assessment report shall be updated whenever new information becomes available which is of importance for the evaluation of the quality, safety or efficacy of the medicinal product concerned.

(*) "

5. Article 8 is replaced by the following :

"Article 8

1. Member States shall take all appropriate measures to ensure that the procedure for granting an authorization to place a medicinal product on the market is completed within 210 days of the date of submitting the application.

2. Where a Member State notes that an application for authorization submitted after 1 January 1993 is already under active examination in another Member State, the former Member State may decide to suspend the detailed examination of the application in order to await the assessment report prepared by the first Member State in accordance with Article 5b."

The Member State concerned shall inform the first Member State and the applicant 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 first Member State shall forward a copy of its assessment report to the Member State concerned.

Within the 90 days of the receipt of the assessment report, the Member State concerned shall recognise the decision of the first Member State. However, if the Member State concerned considers that there are serious grounds for supposing that the authorization of the veterinary medicinal product may present a risk to human or animal health or the environment, it shall inform the first Member State, the Committee for Veterinary Medicinal Products and the applicant within the time limit referred to above, stating its reasons in detail, and apply the procedures laid down in Chapter IV."

6. The following Article 8a is inserted :

"Article 8a

1. With effect from 1 January 1996, where a Member State is informed in accordance with point 13 of the second paragraph of Aricle 5 that another Member State has authorized a veterinary medicinal product which is the subject of an application for authorization in the Member State concerned, that Member State shall forthwith request the authorities of the Member State which has granted the authorization to forward to it the assessment report referred to in the second paragraph of Article 5b. Within 90 days of the receipt of the assessment report, the competent authorities of the Member State concerned shall recognise the authorization granted by the other Member State.

2. Notwithstanding paragraph 1, if the Member State concerned considers that there are serious grounds for supposing that the authorization of the veterinary medicinal product may present a risk to human or animal health or the environment, it shall inform the Member State which granted the initial authorization, any other Member States concerned by the application and the Committee for Veterinary Medicinal Products and the applicant within the time limit referred to in paragraph 1, stating its reasons in detail, and apply the procedures laid down in Chapter IV of this Directive."

7. In paragraph 1 of Article 14, the first sub-parapraph is replaced by the following :

"After an authorization has been issued, the person responsible for placing the product on the market must, in respect of the methods of production and control provided for in points 4 and 9 of the second paragraph of Article 5, take account of technical and scientific progress and introduce any changes that may be required to enable the veterinary medicinal product to be manufactured and checked by means of generally accepted scientific methods. These changes must be accepted by the competent authorities of the Member States concerned.

8. Article 15 is replaced by the following :

"Article 15

1. Authorization shall be valid for five years and shall be renewable for five year periods, on application by the holder at least three months before the expiry date.

2. In exceptional circumstances, and following consultation with the applicant, an authorization may be granted subject to such conditions as appear necessary to ensure the protection of human and animal health or the environment, including specific obligations to conduct further studies following the granting of authorization and specific obligations in respect of the reporting of adverse reactions to the medicinal product."

9. Chapter IV is replaced by the following :

"CHAPTER IV

Committee for Veterinary Medicinal Products

Article 16

1. In order to facilitate the adoption of common Decisions by Member States on the authorization of veterinary medicinal products on the basis of the scientific critieria of quality, safety and efficacy, and to achieve thereby the free movement of veterinary medicinal products within the Community, a Committee for Veterinary Medicinal Products, hereinafter referred to as "the Committee", is hereby set up. The Committee shall consist of representatives of the Member States and of the Commission. The Committee shall be attached to the European Agency for the Evaluation of Medicinal Products established by Council Regulation ../.../EEC, hereafter referred to as the Agency.

2. In addition to the other responsibilities conferred upon it by Community law, the Committee shall examine any question relating to the grant, amendment, suspension or withdrawal of authorization for a veterinary medicinal product which is submitted to it in accordance with the provisions of this Directive.

3. The Committee shall adopt its own rules of procedure.

Article 17

1. In order to obtain the recognition in one or more of the Member States of an authorization issued by a Member State in accordance with Article 4, the holder of the authorization shall submit an application to the competent authorities of the Member State or Member States concerned, together with the information and particulars referred to in Articles 5, 5a and 5b. He shall testify to the identity of the dossier with that accepted by the first Member State, or shall identify any additions or modifications it may contain. In the latter case, he shall certify that the summary of product characteristics proposed by him in accordance with Article 5a is identical to that accepted by the first Member State in accordance with Article 5b.

   Moreover, he shall certify that all the dossiers filed as part of this procedure are identical.

2. The holder of the marketing authorization shall notify the Committee of this application, inform it of the Member States concerned and of the dates of submission of the application and send it a copy of the authorization granted by the first Member State. He shall also send the Committee copies of any marketing authorizations which may have been granted by the other Member States in respect of the product concerned, and shall indicate whether any application for authorization is currently under consideration in any Member State.

3. The holder of the authorization shall also inform the Member State which granted the initial authorization that an application is being made in accordance with this Directive and shall notify it of any additions to the original dossier; that Member State may require the applicant to provide it with all the particulars and documents necessary to enable it to check the identity of the dossiers filed with the dossier on which it took its decision. In addition that Member State shall forward to the Member State or Member States concerned by the application a copy of the assessment report established in accordance with the second paragraph of Article 5b.

4. Each Member State concerned shall recognise the marketing authorization granted by the first Member State within 90 days of receipt of the application. It shall inform the Member State which granted the initial authorization, the other Member States concerned by the application, the Committee, and the person responsible for marketing thereof.

Article 18

1. Notwithstanding Article 17 (4), where a Member State considers that there are serious grounds for supposing that the authorization of the veterinary medicinal product concerned may present a risk to human or animal health or the environment, it shall forthwith inform the applicant, the Member State which granted the initial authorization, any other Member States concerned by the application and the Committee. The Member State shall state its reasons in detail and shall indicate what action may be necessary to correct any defect in the application.

2. All the Member States concerned shall use their best endeavours to reach agreement on the action to be taken in respect of the application. They shall provide the applicant with the possibility to make his point of view known orally or in writing. However, if within 60 days of the expiry of the time limit referred to in Article 17(4), the Member States have not been able to reach agreement they shall forthwith refer the matter to the Committee for the application of the procedure laid down in Article 21.

3. Within the time limit referred to in paragraph 2, the Member State which granted the initial authorization and the other Member States concerned by the application 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. A copy of this information shall be provided to the applicant.

4. As soon as he is informed that the matter has been referred to the Committee, the applicant shall forthwith forward to the Committee a copy of the information and particulars referred to in Article 17 (1).

Article 19

If several applications submitted in accordance with Articles 5 and 5a have been made for marketing authorization for a particular veterinary medicinal product, and Member States have adopted divergent decisions concerning the authorization of the veterinary medicinal product, or its suspension or withdrawal from the market, any Member State or the Commission, or the person responsible for marketing may refer the matter to the Committee for the application of the procedure laid down in Article 21.

The Member State concerned, the person responsible for marketing or the Commission shall clearly identify the question which is referred to the Committee for consideration and, if necessary, shall inform the person responsible for marketing.

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

Article 20

The Member States or the Commission 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 before reaching a decision on a request for a marketing authorization or on the suspension or revocation of an authorization, or on any other amendment to the terms of a marketing authorization which appears necessary, in particular to take account of the information collected in accordance with Chapter VIa of this Directive.

The Member State concerned or the Commission shall clearly identify the question which is referred to the Committee for consideration and shall inform the person responsible for marketing.

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

Article 21

1. 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.

   In case of urgency, on a proposal from its Chairman, the Committee may agree to impose a shorter deadline.

2. In order to consider the matter, the Committee may appoint one of its Members to act as rapporteur. The Committee may also appoint individual experts to advise it on specific questions. When appointing experts, the Committee shall define their tasks and specify the time limit for the completion of these tasks.

3. In the cases referred to in Articles 18 and 19, before issuing its opinion, the Committee shall provide the person responsible for marketing with an opportunity to present written or oral explanations.

   In the case referred to Article 20, the person responsible for placing the medicinal product on the market may be asked to explain himself orally or in writing.

   If it considers it appropriate, the Committee may invite any other person to provide information relating to the matter before it.

   The Committee may suspend the time limit referred to in paragraph 1 in order to allow the person responsible for marketing to prepare explanations.

4. Where the opinion of the Committee is that :

   - the application does not satisfy the criteria for authorization set out in this directive, or
   - the summary of product characteristics proposed by the applicant in accordance with Article 5a should be amended, or
   - the labelling or package of the product is not in compliance with Chapter VII, or
   - the authorization should granted suject to conditions, or
   - an existing marketing authorization should be suspended amended or withdrawn;

   the Agency shall forthwith inform the person responsible for marketing. Within 15 days of the receipt of the opinion, the person responsible for marketing may provide written notice to the Agency that he wishes to appeal. Within 60 days of the receipt of the grounds for appeal, the Committee shall consider whether its opinion shoud be revised, and the reasons for the conclusions reached on the appeal shall be annexed to the assessment report referred to in paragraph 5.

5. Within 30 days of its adoption, the Agency shall forward the final opinion of the Committee to the Commission the Member States and the person responsible for marketing together with a report, describing the assessment of the veterinary medicinal product and the reasons for its conclusions.

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

   a) a draft summary of the product characteristics, as referred to in Article 5a;

b) details of any conditions or restrictions which should be imposed on the supply or use of the veterinary medicinal product concerned, including the conditions under which the veterinary medicinal product may be made available to users;

c) the draft text of the labelling and package leaflet, proposed by the applicant presented in accordance with Chapter VII.

Article 22

1. Within 30 days of the receipt of the opinion of the Committee, the Commission shall prepare a draft of the Decision to be taken in respect of the application taking into account the objectives of Community policies and considering all relevant information. In the event of a draft Decision which envisages the granting of a marketing authorization, the documents referred to in points (a), (b) and (c) of paragraph 4 of Article 21 shall be annexed. The Commission shall transmit the draft Decision to the Member States and to the applicant.

   The Commission shall explain in detail the reasons for any differences between the draft Decision and the opinion of the Committee.

2. The Commission shall adopt the Decision to be taken in respect of the application unless, within 30 days, it has received a reasoned request from a Member State to reconsider the matter. The Member State concerned shall also transmit a copy of its request to the other Member States and the applicant within the same time limit.

3. Within the time limit referred to in paragraph 2, the applicant may submit written observations on the draft Decision for consideration by the Commission.

4. The Commission shall examine any reasoned request received in accordance with paragraph 2, in consultation with the Agency, and after consideration of any further observations submitted by the applicant.

   If the Commission considers that the request raises questions of a scientific or technical nature requiring further examination, it may remit the matter to the Agency. In this case the Committee shall give a second opinion within a time limit of 60 days. Within 30 days of the receipt of the opinion, the Commission shall adopt the Decision to be taken in respect of the application.

   Otherwise the Decision shall be taken in accordance with the procedure laid down in Article 2b and 2c of Directive 81/852/EEC.

5. A Decision adopted in accordance with this procedure shall be addressed to the Member States concerned by the matter and to the person responsible for marketing. The Member States shall either grant or withdraw marketing authorization, or make any adjustment to the terms of a marketing authorization which may be necessary to comply with the Decision within 30 days of its notification. They shall inform the Commission and the Committee thereof.

Article 23

Any application by the person responsible for marketing to amend the terms of a marketing authorization which has been granted in accordance with the provisions of this Chapter shall be submitted to all the Member States which have previously authorized the medicinal product concerned.

The Agency shall, in consultation with the Commission, adopt appropriate arrangements for the examination by the Committee of amendments or variations to a marketing authorization which has been granted in accordance with the provisions of this Chapter.

The procedures laid down in Articles 21 and 22 shall apply mutatis mutandis to variations and amendments of marketing authorizations.

Article 23a

1. Where a Member State considers that the amendment of the terms of a marketing authorization which has been granted in accordance with the provisions of this Chapter or its suspension or withdrawal is necessary, the Member State concerned shall forthwith refer the matter to the Committee for the application of the procedures laid down in Article 21 and and 22.

2. In exceptional cases, where action is urgently necessary to protect human or animal health or the environment, until a definitive Decision is adopted, the Member States suspend the use of the veterinary medicinal product concerned on its territory. It shall inform the Commission no later than the following working day of the reasons for its action.

Article 23b

Articles 23 and 23a shall apply mutatis mutandis to medicinal products authorized by Member States following an opinion of the Committee given in accordance with Article 4 of Directive 87/22/EEC before 1 January 1993.

Article 23c

1. The Agency shall publish an annual report on the operation of the procedures laid down in this Chapter.

2. Within six years of the date referred to in the first sub-paragraph of Article 4 (1), the Commission shall publish a detailed review of the operation of the procedures laid down in this chapter and shall propose any amendments which may be necessary to improve the operation of these procedures.

   The Council shall decide on the Commission proposal within one year of its submission."

10. The third sub-paragraph of paragraph 1 of Article 30 is replaced by the following :

"In the case of veterinary medicinal products imported from a third country, where appropriate arrangements have been made by the Community with the exporting country to ensure that the manufacturer of the veterinary medicinal product applies standards of good manufacturing practice at least equivalent to those laid down by the Community and to ensure that the controls referred to under (b) have been carried out in the exporting country, the qualified person may be relieved of responsibility for those controls."

11. The following Chapter VIa is inserted after Article 42 :

"CHAPTER VIa

Pharmacovigilance

Article 42a

In order to ensure the adoption of appropriate regulatory Decisions concerning the continued authorization of veterinary medicinal products within the Community, having regard to information obtained about adverse reactions to veterinary medicinal products under practical conditions of use, the Member States shall establish a pharmacovigilance system for collecting information about adverse reactions to veterinary medicinal products and for the scientific evaluation of such information.

Article 42b

For the purpose of this Directive, the following definitions shall apply :

- "adverse reaction" shall mean a reaction which is noxious and unintended and which occurs at doses normally used in animals in accordance with the terms of the marketing authorization for the prophylaxis, diagnosis or therapy of disease or for the modification of physiological function.

- "serious adverse reaction" shall mean an adverse reaction which results in death, permanent or prolonged signs or lesions in treated animals.

Article 42c

The person responsible for marketing shall have permanently and continuously at his disposal a person responsible for pharmacovigilance. This person shall be responsible for :

a) the establishment and maintenance of a system which ensures that information about all adverse reactions which are reported to the personnel of the company, including its sales personnel, is collected and collated at a single point;

b) the preparation and submission to the competent authorities of the reports referred to in Article 42d, in such from as may be laid down by those authorities;

c) ensuring that any request from the competent authority for the provision of additional information necessary for the evaluation of the benefits and risks of a veterinary medicinal product is answered fully and promptly, including the provision of information about the volume of sales for the veterinary medicinal product concerned, where relevant;

Article 42d

1. The person responsible for marketing shall be required to record and to report all suspected serious adverse reactions which are brought to his attention by a qualified veterinarian to the competent authorities within 15 days of their receipt.

2. In addition, the person responsible for marketing shall be required to maintain detailed records of all other adverse reactions which are reported to him by a veterinarian health care professional. Unless other requirements have been laid down as a condition of the granting of authorization, these records shall be submitted to the competent authorities immediately upon request or at least every six months during the first two years following authorization and once a year for the following three years. Thereafter, the records shall be submitted at five yearly intervals together with the application for renewal of the authorization, or immediately upon request.

Article 42e

The Member States shall take all appropriate measures to encourage veterinarians to report adverse reactions to the competent authority.

The Member States may impose specific requirements on veterinarians, in particular in respect of the reporting of serious or unexpected adverse reactions, or where such reporting is a condition of the marketing authorization.

Article 42f

The Member States shall ensure that reports of serious adverse reactions are brought to the attention of the Agency and the person responsible for marketing within 15 days of their receipt.

Article 42g

In order to facilitate the exchange of information about pharmacovigilance within the Community, the Agency shall, in consultation with Member States, the Commission and interested parties, draw up detailed guidance on the collection, verification and presentation of adverse reaction reports.

Article 42h

Where as a result of the evaluation of adverse reaction reports, a Member State is considering amending the terms of a marketing authorization or its suspension or withdrawal, it shall forthwith inform the Agency.

In case of urgency, the Member State concerned may suspend the marketing of a medicinal product, provided the Agency is informed at the latest on the following working day."

Article 29h

Where as a result of the evaluation of adverse reaction reports, a Member State is considering amending the terms of a marketing authorization or its suspensions or withdrawal, it shall forthwith inform the Agency.

In case of urgency, the Member State concerned may suspend the marketing of a medicinal product, provided the Agency is informed at the latest on the following working day."

Article 4

Member States shall take all appropriate measures to comply with the provisions of this Directive, with the exception of Article 1 (6), before 1 January 1993. They shall forthwith inform the Commission thereof.

Member States shall take all appropriate measures to comply with Article 1 (6) of this Directive before 1 January 1996. They shall forthwith inform the Commission thereof.

When Member States adopt these provisions, these shall contain a reference to this Directive or shall be accompanied by such reference at the time of their official publication. The procedure for such reference shall be adopted by Member States.

Article 5

This Directive is addressed to the Member States.

Done at Brussels For the Council

Proposal for a

COUNCIL DIRECTIVE

repealing Directive 87/22/EEC on the approximation of national measures relating to the placing on the market of high technology medicinal products particularly those derived from biotechnology

Proposal for a

COUNCIL DIRECTIVE

repealing Directive 87/22/EEC on the approximation of national measures relating to the placing on the market of high technology medicinal products particularly those derived from biotechnology

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community, and in particular Article 100a thereof;

Having regard to the proposal from the Commission(1),

In cooperation with the European Parliament(2)

Having regard to the opinion of the Economic and Social Committee(3)

Whereas the provisions of Council Directive 87/22/EEC(4) have now been superseded by the provisions of Regulation (EEC)..../.. of ..... laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products(5) and by Council Directive 88/182/EEC of 22 March 1988 amending Directive 83/189/EEC laying down a procedure for the provision of information in the field of technical standards and regulations(6);

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(1)

(2)

(3)

(4) OJ No L 15, 17.1.1987, p. 38.

(5)

(6) OJ No L 81, 26.3.1988, p. 75.

Whereas provision has been made in Council Directive ../.../..[7] for the continued management of marketing authorizations which have been granted by Member States following the opinion of the Committee for Proprietary Medicinal Products given in accordance with Directive 87/22/EEC;

Whereas, furthermore, provision has been made in Council Directive ../.../..[8] for the continued management of marketing authorizations which have been granted by Member States following the opinion of the Committee for Veterinary Medicinal Products given in accordance with Directive 87/22/EEC;

Whereas Directive 87/22/EEC should therefore be repealed;

Whereas in the interests of legal certainty, provision should be made for the continued examination of applications for marketing authorization which have been referred to Committee for Proprietary Medicinal Products or the Committee for Veterinary Medicinal Products in accordance with Directive 87/22/EEC before 1 January 1993,

HAS ADOPTED THIS DIRECTIVE :

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(7)

(8)

Article 1

With effect on 1 January 1993, Council Directive 87/22/EEC is repealed.

Article 2

Applications for marketing authorization which have been referred to the Committee for Proprietary Medicinal Products or to the Committee for Veterinary Medicinal Products before 1 January 1993 in accordance with Article 2 of Directive 87/22/EEC and in respect of which the Committee concerned has not given an opinion by 1 January 1993 shall be considered in accordance with Regulation (EEC)..../..

Article 3

Member States shall take all appropriate measures to comply with this Directive before 1 January 1993. They shall forthwith inform the Commission thereof.

When Member States adopt these provisions, these shall contain a reference to this Directive or shall be accompanied by such reference at the time of their official publication. The procedure for such reference shall be adopted by Member States.

Article 4

This Directive is addressed to the Member States.

Done at Brussels For the Council

COMPETITIVENESS AND EMPLOYMENT IMPACT STATEMENT

COMPETITIVENESS AND EMPLOYMENT IMPACT STATEMENT

relating to the proposals for the future system for the free movement of medicinal products in the European Community

I. What is the main reason for introducing the measures ?

Completion of the internal market; harmonization of individual administrative decisions concerning the authorization and conditions of use of medicinal products;
establishment of Community authorization procedures for certain categories of innovatory medicinal products;
establishment of a European Medicines Evaluation Agency to advise the Community institutions and Member States on scientific issues relating to the quality, safety and efficacy of medicinal products; improvement of the protection of public health, in particular in respect of the monitoring of adverse reactions to medicinal products (pharmacovigilance).

II. Features of the business in question :

These measures primarily concern pharmaceutical manufacturers.

Because of the high costs of developing new medicinal products, in excess of 100 million ECU for a major innovatory product, pharmaceutical companies are often large multinational companies, and there is currently a significant increase in concentration in this sector as companies seek to attain the "critical mass" perceived as necessary to finance research and development.

There are also a number of smaller or medium sized companies, geared primarily to national or regional markets, manufacturing conventional medicinal products or copies of products whose patent has expired.

In addition, there are a very limited number of small, highly innovatory research-based companies, concentrating on basic research into new therapies.

III. **What direct obligations does this measure impose on business ?**

The majority of this package is procedural and it imposes few new direct obligations on business.

Although manufacturers of medicinal products derived from biotechnology will be required to obtain authorization from the Community, rather than Member States, it should be noted that these products are already subject to a compulsory Community coordination procedure, based on harmonized Community requirements, and the new requirements will not therefore result in any increase in the cost of preparing applications. For other categories of innovatory medicinal product, the centralized procedure will be available on an optional basis, as an alternative to national procedures.

For other categories of medicinal products, the use of the decentralized Community procedure will become compulsory after 1996. However, since the requirements for the preparation of applications for authorization are already harmonized, there should be no increase in the overall costs of obtaining authorization.

Although the pharmaceutical industry will be expected to pay fees for of authorization, the detailed fee structure will only be adopted following consultation of the industry, and in no case will the fees payable to the Community exceed the sum of the fees currently payable to the individual Member States.

Finally, each company will be required to establish a system for collecting and evaluating reports of adverse reactions (ADRs) to its medicinal products and for reporting ADRs rapidly to the regulatory authorities. Although such requirements are new at the Community

level, they already exist in most Member States, and even where formal requirements are not laid down, most reponsible companies have arrangements for collecting and assessing such information.

IV. **What indirect obligations are local authorities likely to impose on business ?**

None foreseen.

V. **Are there any special measures in respect of SMEs ?**

No.

VI. **What is the likely effect on :**

a) **the competitiveness of business ?**

The proposed measures will facilitate the access of all medicinal products to a Community scale market. They are likely to be of particular benefit to smaller scale companies who lack the resources to establish local subsidiaries in the different Member States to deal directly with national regulatory authorities. In consequence, some companies may have to make efforts to maintain their competitiveness vis-à-vis companies established elsewhere in the Community.

b) **employment ?**

No significant effect is anticipated.

VII. **Have both sides of industry been consulted on these proposals ?**

Extensive consultation has preceded the preparation of these proposals. In its March 1988 report on the activities of the Committee for Proprietary Medicinal Products (COM (88) 143) the Commission invited all interested parties to submit comments on the general orientation to be followed in these proposals. In addition, two furhter staff papers of April 1989 and December 1989 have summarized the state of the consultation process and invited comments on specific aspects of the proposals.

Those consulted include :

- associations of the pharmaceutical industry (human and veterinary);
- associations of consumers;
- associations of veterinarians, doctors and pharmacists;
- chemical industry trade unions.

FINANCIAL STATEMENT

FINANCIAL STATEMENT

Future system for the free movement of medicinal products within the European Community

1. Budget Headings

N° A 1 and A 2 Expenses of officials and other staff

N° A 2510 Committee (obligatory consultation) expenses

N° B 5300 [ex B 7750] and B 5302 (*)
Actions for the internal market

(*) A new budget heading to be inserted in Part B of the Budget : "Operational expenses of the European Agency for the Evaluation of Medicinal products."

2. Legal basis

Article 100 A of the EEC Treaty.

3. Description of the project

3.1. General objective

Realisation of the internal market for medicinal products for use in human beings or animals. Improvement of the protection of public health throughout the Community.

3.2. Specific objectives

a) the establishment of a new autonomous European Agency for the Evaluation of Medicinal Products; the new Agency will be made up of the existing Committee for Proprietary Medicinal Products (CPMP) and the Committee for Veterinary Medicinal Products (CVMP), with substantial additional logistical and administrative support. The expenses for these two committees (CPMP and CVMP) currently in the budget (line 2510) will therefore become part of the Agency budget (cost in 1989 was 117,000 ECU). Its task will be to coordinate the work of evaluation and supervision of medicinal products being conducted in Member States to avoid duplication of effort, but at the same time ensure that all relevant factors are taken into consideration during the authorization process;

b) the creation of a new centralized Community procedure, compulsory for biotechnology products and veterinary medicines used as performance enhancers, and available on an optional basis for other innovatory medicinal products, leading to a Community authorization, valid throughout all 12 Member States, which will subsequently be managed and supervised by the Community institutions;

c) the creation of a new decentralized procedure, based on the principle of mutual recognition, which will allow the progressive extension of a marketing authorization from one Member State to the others, with important safeguards to ensure that there is no dilution of the strict standards of quality, safety and efficacy. In the event of a disagreement between Member States about the quality, safety or efficacy of a medicinal product, the Agency will provide an independant scientific evaluation of the issues involved, and a binding arbitration procedure at Community level will follow. However, the monitoring of the product will remain the responsibility of the individual Member States.

d) the establishment of reinforced Community procedures for the collection and evaluation of adverse reaction reports about medicinal products and for the adoption of appropriate regulatory action about such reports.

e) coordination of the exercise by Member States of the various supervisory responsibilities concerning the manufacture and testing of medicinal products, in particular :

- good manufacturing practices
- good laboratory practices
- good clinical practices

f) the maintenance of a pharmaceutical data base which is available for public use.

g) the provision of scientific advice on maximum residue levels for veterinary medicines which may be accepted in foodstuffs of animal origin without risk for the consumer.

4. Justification of the project

4.1. Justification of the type of project proposed

The experience acquired during the operation of the existing Community concertation procedure for high technology/biotechnology medicinal products (Directive 87/22/EEC) has clearly demonstrated the need to pool the resources of the Member States in order to ensure the rapid but exhaustive evaluation of applications. The sheer complexity of applications for authorization for these types of products, which cost over 100 million ECUs to assemble and run to tens of thousands of pages means that the duplication of effort and waste of scarce scientific resources resulting from independant national evaluations can no longer be tolerated. It is therefore necessary to bring together the best available scientific experts currently working within the Member States to evaluate applications on behalf of the Community as a whole within the framework of a European Medicines Evaluation Agency.

For other categories of medicines, experience suggests that a decentralized procedure, based on the principle of mutual recognition may be feasible. However, because of the important public health issues involved, it is clear that important safeguard clauses are required by Member States, and there can be no question of automatic mutual recognition. The continued need for safeguard clauses implies that the Community must be provided with the administrative, technical and scientific resources to arbitrate in the event of a disagreement between Member States, leading to binding decisions.

For practical and managerial reasons, it is considered that the task of preparing the necessary advice should be devolved to an autonomous Agency. However, the final decisions to be taken must be reached within the existing institutional mechanisms.

4.2. Interest in the project at Community level

The realisation of the internal market implies that all categories of industrially prepared medicinal products should be allowed to circulate freely throughout the Community. The Community must therefore be provided with the means to reconcile differences between Member States regarding the acceptance of products, while maintaining the high standards necessary for the protection of the European patient.

5. Financial implications

5.1. General remarks

a) The operational expenses of the new Agency will be covered :

- in part by fees paid by pharmaceutical enterprises for the evaluation of applications. The Commission intends to propose to Council a special financial regulation for the Agency which will include a scheme of fee income for marketing authorization. It is intended that fee income will ultimately provide the major source of financing for the Agency;

- in part by funding from the Community budget, through a new budgetary line to be inserted in the operational part of the budget (Part B). The form of Community funding of the Agency will be defined by the Commission proposal for the Agency's financial regulation.

b) Approximative estimates of the financial expenditure involved are given for illustrative purposes in section 5.2. below. In order to provide more precise estimates of the cost of the Agency, and the anticipated income from fees paid by the industry, a study will be requested from an external consultant, to be completed before the end of 1991. The estimates in section 5.2 in no way prejudge the level of Community financing once the Agency is operational.

c) The Commission itself will also have new tasks resulting from the introduction of the new procedures, and it is therefore necessary to provide the resources required (section 5.3. below).

d) Both the level of Community funding of the Agency and the resources required from the administrative appropriations of the Commission will be determined annually in the course of the budgetary procedure and will be entirely compatible with financial perspectives.

5.2. Financial implications : The European Agency for the Evaluation of Medicinal Products

Year	N°	Amount	Purpose
1991	B 5300 [ex B 7750]	200.000 ECU	Preliminary study
1992	B 5306 (*)	2.000.000 ECU (**)	Establishment of the Agency
1993	B 5306 (*)	p.m.	Contribution from the Community to the operational expenses of the Agency.

(*) New budgetary line

(**) This is an indicative amount which will be proposed in the course of the 1992 budgetary procedure by the Commission.

The operational expenses of the Agency will be estimated in detail following the preliminary study which is to be completed before the end of 1991. Approximative costs and estimates of the resources necessary are given below for illustrative purposes on an annual basis.

5.3. Financial implications : services of the Commission

The new procedures require that the Commission, assisted by a regulatory committee, adopt the final decisions on the grant, refusal or amendment of auhorization, pharmacovigilance alerts, tolerances for residues of veterinary medicinal products, etc. Additional resources will be required for this purpose, to be provided either through internal redeployment or within the framework of the budgetary procedure.

The number of decisions to be taken each year has been evaluated as follows :

	1993	1994	1995
Community authorizations : human and veterinary (centralized procedure)	30	45	60
Variations to Community authorizations	20	60	150
Arbitrations (decentralized procedure)	100	150	120
Pharmacovigilance alerts	50	75	100
Tolerances for residues of veterinary medicines	20	30	40

The estimated additional requirements are :

1. Personnel (N° A 1 and A 2)

1991 : + 2A + 1B + 2C : Preparation and establishment of the Agency; participation in the preliminary study
1992 : + 2A + 1B + 2C : Establishment of the Agency
1993 : + 1A + 1B + 1C : Management of centralized and decentralized decisions.

Total 5A 3B 5C

Total cost (at 80.000 ECU per average) is 400.000 ECU in 1991; 800.000 ECU in 1992 and 1.040.000 ECU from 1993.

2. Meetings (N° A 2510)

In the event of an objection from one or more Member States, the draft Commission decision will have to be submitted to a regulatory committee for approval. Two new regulatory committees are necessary from 1993, one for medicinal products for human use, one for veterinary medicinal products, meeting at approximately 2 monthly intervals.

1993 : 120.000 ECU (10.000 ECU x 12 meetings).

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